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To my father… who is gone.

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A Hypothesis of Circulating MicroRNAs' Implication in High Incidence of Atrial Fibrillation and Other Electrocardiographic Abnormalities in Cancer Patients

Nikolaos Kapodistrias, Georgia Theocharopoulou, and Panayiotis Vlamos

1 Introduction

MicroRNAs (miRNAs) are evolutionary conserved, single-stranded, non-coding RNA molecules that bind target messenger RNA (mRNA) to prevent protein production. They are endogenously expressed, and typically 19–25 nucleotides in length. They are initially generated as long primary miRNAs (pri-miRNAs) by RNA II polymerase-mediated transcription in the cell nucleus. The primary miRNAs are cleaved into approximately 70 nucleotide-long precursor miRNAs, which are subsequently transported into the cytoplasm and further cleaved into mature miRNAs (Kim 2005). Mature miRNA is generated through two-step cleavage of primary miRNA (pri-miRNA), which incorporates into the effector complex RNA-induced silencing complex (RISC). The miRNA functions as a guide by base-pairing with target miRNA to negatively regulate its expression by binding in the 3′ untranslated region. The level of complementarity between the guide and the mRNA target determines which silencing mechanism will be employed, either cleavage of target messenger RNA (mRNA) with subsequent degradation or translation inhibition (Bartel 2004; Perron and Provost 2008). Thus, in mammals, miRNAs are estimated to control the activities of more than 50% of all protein coding genes (Krol et al. 2010) and are involved in the regulation of almost all cellular processes (Huang et al. 2011).

Many of the mature miRNAs are remarkably stable in the extracellular harsh environment, despite the presence of high RNA's activity and were also discovered in cell-free blood plasma and serum (Chen et al. 2008). The existence of

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extracellular circulating miRNA in all other biological fluids was also confirmed (Hanke et al. 2010). MiRNAs are released from cells into circulation by using several packaging and transportation systems in order to avoid degradation encasement in extracellular membrane vesicles such as exosomes (30–100 nm) or microvesicles (50–1000 nm) (Mause and Weber 2010; Valadi et al. 2007). They are also secreted via binding to miRNA-binding proteins, such as AGO2, or serum lipid carriers such as HDL (Arroyo et al. 2011; Vickers and Remaley 2012). Moreover, miRNAs are passively involved in shedding vesicles, such as apoptotic bodies (−4000 nm), as a result of apoptotic death (Zernecke et al. 2009). Evidence suggests that extracellular miRNA species might carry cell–cell signaling function during various physiological and pathological processes (Turchinovich et al. 2013). Although many experiments show exosome- and microvesicles-mediated transfer of extracellular miRNAs and subsequent genetic and phenotypic changes in the recipient cells, it has recently been challenged again whether the concentration of exosomal miRNAs in bio-fluids is sufficient to carry a translational repression of their target genes in the recipient cells (Chevillet et al. 2014).

2 Circulating MicroRNAs

Accumulating evidence has revealed that microRNAs are extensively involved in cancer development, progression, and suppression, by regulating thousands of cancer-associated genes (Di Leva et al. 2014). Circulating miRNAs were first detected in the cancer patients' serum and plasma (Chen et al. 2008; Mitchell et al. 2008) in 2008, and subsequently found in a variety of bodily fluids such as saliva, urine, pleural effusions, and cerebrospinal liquid (Weber et al. 2010). Evidence suggests that miRNAs can be transferred from one cancer cell to another through the exchange of exosomes. Thus, it is hypothesized that vesicle-enwrapped extracellular miRNAs may function as an intercellular communication system in the body, but their role in cancer progression and metastasis remains unclear (Valadi et al. 2007). Some in vitro studies have shown that extracellular miRNAs can be transferred from one cell to another through exosomes and in the recipient cells they can downregulate their target genes (Kogure et al. 2011; Montecalvo et al. 2012; Sohel et al. 2013). Observations in in vitro models corroborate the influence that the delivery of extracellular miRNAs can exhibit on gene expression (Cui et al. 2016; Fujita et al. 2015; Mao et al. 2016; Skog et al. 2008; Zhang et al. 2016). More important, in another study, tumor-derived exosomes containing miR-21 (over-expressed in most tumors in plasma) and miR-29a, upon transfer to immune cells, can bind and activate Toll-like receptors 7 (TLR7) and 8 (TLR8), which ultimately trigger a pro-metastatic inflammatory response that may lead to tumor growth and metastasis (Fabbri et al. 2012).

In current liquid biopsy studies that evaluate circulating miRNA in various cancer types, important facts with diagnostic and prognostic significance emerge

(Larrea et al. 2016). One of the most recent studies confirms that miRNAs with crucial roles in cancer growth and progression in tissues exist in circulating form (He et al. 2015). Of these miRNAs, two were frequently increased in most cancer tissues. The higher concentrations of miR-20a-5p and miR- 21-5p in the cells increase cancer's invasion and metastatic potential. Whether the increased miR-20a-5p (member of the 17–92 miRNA cluster) and miR-21-5p concentrations in circulation are a direct result of tumor burden is yet to be determined. MiR-21 is expected to target several key genes involved in cell proliferation (PTEN, a tumor suppressor), and could promote invasiveness by targeting inhibitors of matrix metalloproteinases (RECK and TIMP3) in cancer cells (Gabriely et al. 2008).

Furthermore, miR-20a-5p pertain to an important set of miRNAs (cluster 17–92) that modulates the cell cycle, proliferation, and apoptosis through interactions with key genes like E2F1 (E2F transcription factor 1) and BCL2 (B-cell CLL/lymphoma 2), an apoptosis regulatory protein (Luo et al. 2016). Many studies correlate levels of circulating miRNAs with tumor burden and stage. Even in early tumor stages, when levels normalize after curative resection or chemotherapy, they can then increase again with progression of the disease (Chen et al. 2014; Hill et al. 2013). Finally, in one report the circulating miR-21, which is upregulated in most malignancies, showed the highest upregulation in exosomes (primary tumor tissues) and liver metastasis tissues in colorectal cancer cases, reflecting the TNM stage and indicating the broad tumor burden associated with higher circulating miRNA levels (Tsukamoto et al. 2017).

Taking into account that in advanced stages tumors with wide tumor volume are linked with higher levels of circulating miRNAs, begs the question whether these miRNAs exert their influence in gene repressive action, not only in tumor tissues in local or metastastic sites (Alečković and Kang 2015) but also in normal cells at distant tissues affecting thus, vital functions and organs. Cachexia is such an example in which provocative mechanisms have been proposed, indicating an active role of extracellular circulating miRNAs in this phenomenon. Precisely, tumor-derived microvesicles induce apoptosis of skeletal muscle cells. This pro-apoptotic activity is mediated by a microRNA cargo, miR-21, which signals through the Toll-like 7 receptor (TLR7) on murine myoblasts to promote cell death. Furthermore, tumor microvesicles and miR-21 require c-Jun N-terminal kinase activity to regulate this apoptotic response (He et al. 2014). In addition, excessive proteolysis in cachexia, a common consequence in diseases such as cancer, diabetes, chronic heart failure, and aging, could be explained from in vivo gain and loss of function. Experiments revealed that miRNA-206 and miRNA-21 were sufficient and required for atrophy. In silico and in vivo approaches identified transcription factor YY1 and the translational initiator factor eIF4E3 as downstream targets of these miRNAs (Soares et al. 2014). Such an assembly could clarify the mode of action of extracellular miRNAs and their potency in systemic tissue genes interference and repression.

3 MicroRNAs in Atrial Fibrillation and Remodeling

Recent studies point out an increase of atrial fibrillation incidence in cancer patients, but the underlying mechanisms linking atrial fibrillation and cancer are still unclear (Mery et al. 2017). Notably, the prevalence of AF appears to be higher among patients with cancer at the time of diagnosis, even before undergoing therapy, indicating the preexistence of an underlying molecular pattern (O'Neal et al. 2015). The involution of circulating miRNAs-exosomes in the serum or plasma of metastatic patients at such a cardiac rhythm disturbance has never been studied rigorously in the past.

MicroRNAs' expression in atrial tissues in the presence of atrial fibrillation in the general population has been detected in a variety of studies, suggesting a possible impact in their generation (van den Berg et al. 2017). Myocardial miRNAs that were consistently upregulated in three or more studies were miR-15b, miR-21, miR-24, miR-30a, miR-142- 3p, miR-146b, miR-208b, miR-223, and miR-499. Furthermore, in one study, miR-21 was downregulated in right atrial (RA) tissue, but upregulated in left atrial (LA) tissue, a fact that can explain the various tissues' origins (Liu et al. 2014).

Explorative studies have implicated miRNAs in predisposition of AF by induced remodeling processes which involve ion channel remodeling, Ca2+ overload, structural remodeling such as fibrosis and autonomic dysregulation (Schotten et al. 2011). In AF patients, and a goat model of AF, miR-31 upregulation that suppresses an upstream regulator of several ion channels was described (Reilly et al. 2016). Moreover, miR-328, linked with decreasing Cav1.2, Cav 1, and ICaL, shortening of the action potential duration and enhancing AF susceptibility, was the highest upregulated miRNA in a microarray analysis of left atrium tissue of AF patients as well as in a canine atrial tachypacing model (Lu et al. 2010). A microarray screening of patients with AF and without AF identified miR-208a and miR-208b as the most significantly increased miRNA in AF. Further analysis confirmed CACNA1C and CACNB2 as direct targets of miR-208a/b (Cañón et al. 2016). Additionally, miR-21 was upregulated in right atrium cardiomyocytes of AF patients and correlated with decreased CACNA1C and CACNB2 levels (Barana et al. 2014). MiR-1 is a muscle-specific miRNA and the most abundantly expressed miRNA in both ventricles and atria. MiR-1 was found upregulated and, at the same time, decreased levels of KCNE1 and KCNB2 mRNA and protein, shortening of the atrial effective refractory period, and increase of AF susceptibility, expressing pro-arrhythmogenic effects, were observed (Kakimoto et al. 2016). Furthermore, miR-30d was found to be highly expressed in patients with persistent AF, corresponding to downregulation of KCNJ3 and Kir3.1 (Morishima et al. 2016). Finally, other microRNAs are shown to be involved in high atrial rates during AF, causing a Ca2+ overload and an imbalance in intracellular Ca2+ homeostasis, which contribute to AF perpetuation. An inverse correlation between the upregulation of miR-208b, but not of miR-208a, and a decrease in sarcoplasmic reticulum Ca2+ adenosine triphosphates type 2a (SERCA2) mRNA in atrial myocytes in AF and control patients has been observed

(Cañón et al. 2016). Atrial fibrosis is considered the basic condition of atrial structural remodeling in AF and may promote reentry by conduction slowing, increased anisotropy, or unidirectional conduction block (Souders et al. 2009). Furthermore, fibroblasts, by interactions with cardiomyocytes, affect excitability and thereby conduction velocity (Adam et al. 2012). Upregulation of miR-21, highly expressed in fibroblasts, has been associated with increased cardiac fibrosis, mediating this process (He et al. 2016; Huang et al. 2016). MiR-21 also promotes STAT3 phosphorylation through the targeting of the protein inhibitor of activated STAT3 (PIAS3) in multiple myeloma cells and the inhibition of antagomir-21 in rats with pericarditis and AF (Xiong et al. 2012). MiR-146b-5p was also upregulated in AF patients along with an increase in MMP-9 and collagen content. On the other hand, TIMP-4 was downregulated. TIMP-4 was established as a direct target of miR-146b-5p. Transfection of miR-146b-5p in cardiac fibroblasts reduced TIMP-4 and increased collagen content (Wang et al. 2015). MiR-208a and miR-208b have frequently been implicated in AF pathophysiology for their role in Ca2+ -handling and calcium channel regulation. However, these miRNAs are much better known for their role in structural remodeling in cardiovascular disease. Transgenic mice overexpressing miR-208a developed cardiac hypertrophy with suppressed expression of the targets thyroid hormone-associated protein (Thrap1, a known repressor of MYH7 transcription) and myostatin (a known repressor of muscle growth) (Callis et al. 2009). Inhibition of this miRNA in several HF models has successfully prevented the formation of both cardiomyocyte hypertrophy and fibrosis (Montgomery et al. 2011); therefore, miR-208 should be considered as a potential target for AF therapy. Finally miR-199a, not implicated in the regulation of a specific ion channel or extracellular matrix genes, in AF was found upregulated to suppress and target FKBP5 (Chiang et al. 2015). FKBP5 may interact with heat shock protein and may be involved in stabilizing microtubules and intracellular trafficking. However, FKBP5 may also affect Ca2+ -regulation, but its function in AF pathogenesis has not yet been demonstrated (Cioffi et al. 2011).

4 Discussion

Circulating forms of microRNAs in cancer patients have been analyzed as biomarkers in many studies but little is known about their effects in disorders that develop in normal tissues in cancer patients. Their mode of function implies that most of them have an active role in cancer progression and metastasis as well as in deregulation of normal processes. The high levels of miRNAs in plasma or serum, which are predictably higher in patients with extensive disease and wide tumor burden, are anticipated to have an impact on crucial functions and organs. The way that circulating miRNA can spread through the fluids in other tissues could be considered a kind of "transfection" that targets the recipient cells and produces changes in host genes, affecting their function. As depicted above, many miRNAs in heart atrial tissues are over-expressed and implicated in pre-arrhythmogenic conditions as well as

fibrillation emergence, affecting ion channel remodeling. More importantly, they pose atrial structural remodeling and promote fibrosis. The most upregulated mirRNAs that have been established to exert these deregulatory actions in atrial tissues were miR-328, miR-31, miR-208, miR-1, miR-30d, miR-146b, miR-199a, and most importantly the miR-21. Most of these mirRNAs detected in various cancer types studies, circulating in serum or plasma, were found upregulated and correlate with major diagnostic and prognostic significance (Le et al. 2012; Ma et al. 2017; Nonaka et al. 2014; Selth et al. 2013; Tang et al. 2016; Ulivi et al. 2013). Notably, miR-21, the most abundant miRNA, at high levels in tissue or fluids of cancer patients, with multiple roles and targets, is present in almost all types of epithelial malignancies. This enhances the possibility that these microRNAs, pass through the atrial tissue and apply their repressive effects in genes that control cardiac conduction, producing arrhythmias. In this context, miR-21 dependent atrial fibrillation is theoretically feasible, something that previously has been confirmed in transfection laboratory tests. However, further experimental confirmation is needed. Finally, other electrocardiograph abnormalities could be specified in cancer patients via a miRNA regulatory manner. An electrocardiographic signature could be associated with specific miRNA panel, especially in high-volume disease patients.

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Central-Line-Associated Bloodstream Infections (CLABSIs) Incidence and the Role of Obesity: A Prospective, Observational Study in Greece

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1 Introduction

The central venous catheters (CVCs) are an integral part of the care of adult patients in Intensive Care Units (ICU), providing vascular access for the administration of fluids, drugs, nutrition, blood products as well as hemodynamic monitoring and blood sampling (Kim et al. 2011). Approximately 48% of all ICU patients have central venous catheters or about 15 million catheterization days per year (Center for Disease Control and Prevention 2011). Although central venous catheters provide reliable vascular access, there are several risks linked with their use. The most common risk associated with the existence of central venous catheters is the CLABSI, caused by microorganisms that colonize the external surface of the device or the lumen through which the fluid passes when the device is inserted or during its use (Institute for Healthcare Improvement 2012).

CLABSIs are defined as laboratory-confirmed blood-borne infections associated with the presence of central venous catheters, provided that the central venous catheter has been placed at least 48 h prior to the onset of the infection with no apparent source other than the CVC (O'Grady et al. 2011). The estimated CLABSI rate in

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ICU in the United States is 0.8 per 1000 center line days (Hallam et al. 2018). According to the Institute for Health Care Improvement, in 2012, about 90% of all CLABSIs occurred due to the use of central venous catheters, resulting in increased hospitalization duration, increased costs, and increased mortality rates. CLABSIs are among the most important hospital infections in the ICU, accounting for 10–20% of all hospital-acquired infections (Bianco et al. 2013). These infections are the leading cause of death with reported mortality rates in adult ICU patients from 12% to 25% (Marra et al. 2010). CLABSIs are an important source of morbidity and mortality that in the United States account for about 28,000 annual deaths (Lissauer et al. 2012). In addition, CLABSIs contribute to a significant financial burden on health care institutions by extending the duration of hospitalization for about seven days at an additional cost of approximately $ 45,000 (Lissauer et al. 2012).

CLABSIs can usually be prevented by applying the indicated guidelines (Kusek 2012). Therefore, many Health Organizations have made efforts to reduce the incidence of CLABSIs. Such changes include the use of cessation-based insertion links (Lissauer et al. 2012) and in particular (1) hand hygiene before the use of chlorhexidine for skin antisepsis, (2) avoidance of the femoral vein for insertion of the catheter, and (3) direct removal of the catheters, when it is no longer advisable to use them (Agency for Healthcare Research and Quality 2013).

The purpose of this study was to investigate the incidence of obesity in the development of central venous catheter infections.

2 Materials and Methods

This is a prospective, observational study. The data were collected in the ICUs of three major hospitals in Greece during a period of 18 months. Totally, 744 patients were included in the study.

2.1 Exclusion Criteria

During the study, 224 patients were excluded. The exclusions criteria were:

- Catheterizations performed in patients who died within 48 h of their admission to ICU ($n = 211$)
- Patients whose BMI could not be calculated ($n = 8$)
- Patients who did not have a disease severity score (APACHE II, MODS) ($n = 5$)

Patient demographics, body mass index (BMI), APACHE II, and MODS score were recorded. The patient's height was measured from his/her bed with a specific measuring scale, while his/her weight was measured by a special crane scale that existed as equipment in the ICU. In order to ensure the validity and reliability of the measurements, the cranes in all three hospitals were calibrated daily.

An attempt to introduce the central venous catheter was considered when the catheter's needle punctured the patient's skin. As soon as the doctor pierced the patient's skin, time recording began. In order to ensure the validity of the measurements and to ensure the reliability of the time measurement, the same timer was used in the three ICUs.

2.2 Statistical Analysis

The statistical analysis was carried out using IBM SPSS 21.0 statistical package. Categorical data are presented in absolute and relative frequencies. Numerical data are described by median and standard deviation (SD). Kolmogorov–Smirnov test was used for the normality of the distribution of numerical variables. Differences in categorical variables were determined by a chi square test and by Fisher's exact test, while Student's t-test was used to test the differences in numerical variables. Also, the differences in variables that deviate from normal distribution were tested by the Mann–Whitney U test. All P values were two-sided, and the level of significance was set at $p = 0.05$. Multivariate regression binary logistic analysis was used for the predictors of CLABSIs.

3 Results

The study included 744 ICU patients aged 63.6 ± 16.6 years. The Apache II score and MODS score of patients were 23.3 ± 6.9 and 7.5 ± 3.8, respectively. Totally, 512 (68.8%) patients were admitted to ICU from a clinic, 188 (25.3%) patients from the Emergency Department and 44 (5.9%) patients from another ICU. The demographics and clinical characteristics of the patients are presented in Table 1.

The number of doctors' attempts to place the central venous catheter was 3.4 ± 2.8, while the catheterization duration was 11.8 ± 11.3 min. The days of hospitalization on catheterization were 9.6 ± 9.6 days.

Totally, 5.426 catheter-days were included in the study. Among the 722 CVCs, 178 (24.7%) were CLABSIs. The incidence rate of CVC-associated CLABSI was 22.48 infections per 1000 catheter-days.

The main cause of CLABSI was pseudomonas (29.4%), followed by Acinetobacter (22.2%), Klebsiella (10.3%), Candida (9.3%), enterococcus (7.2%), E. Coli (6.7%), Staphilococcus (5.2%), Proteus (4.6%), MRSA (2.1%), Pneumoniococcus (1.5%), and Hemophilus (1.5%).

The duration of hospitalization of patients in the ICU was 19.4 ± 12.8 days and the total hospitalization was 24.8 ± 12.8 days. Of all the patients, 316 (43.8%) survived and 406 (56.2%) died. At 28 days, 204 (28.3%) patients were discharged, 256 (35.5%) patients have died, and 262 (36.3%) remained in the hospital.

Table 1 Demographics and clinical characteristics of the sample

Variables		N (%)
Gender	Male	376 (50.5)
	Female	368 (49.5)
	Respiratory	348 (46.8)
	Surgical	216 (29)
Diagnosis	Infection	68 (9.1)
	Cardiology	56 (7.5)
	Medical	56 (7.5)
	Underweight	52 (Hallam et al. 2018)
	Normal	348 (46.8)
BMI, kg/m^2	Overweight	256 (34.4)
	Obese	72 (9.7)
	Morbidity obese	16 (2.2)
Comorbidity	Diabetes mellitus	124 (16.7)
	Cancer	128 (17.2)
	Jugular vein	450 (62.3)
CVC site	Subclavian vein	184 (25.5)
	Femoral vein	88 (12.2)
Type of CVC	Antimicrobial	636 (88.1)
	Non-antimicrobial	86 (11.9)

CVC central venous catheter

Among the CLABSI and no CLABSI groups, we found statistically significant difference concerning the diagnosis, BMI, comorbidity, CVC site, CVC type, N attempts for catheterization, doctors' experience, catheterization duration, MODS score, LOS ICU, total LOS, as well as the outcome and 28 days' outcomes. The results of the univariate analysis are shown in Table 2.

The variables that were related to the CLABSIs were entered into the multivariate binary regression model. CLABSI was significantly predicted by the BMI (p = 0.001), by the diabetes mellitus as comorbidity (p = 0.013), by the doctors' experience (p = 0.001), by the type of CVC (p = 0.001) and the CVC site (p = 0.001), by the number of efforts for CVC insertion (p = 0.009), by the catheterizations' duration (p = 0.001) and by the MODS score (p = 0.001). The findings of binary regression are shown in Table 3.

4 Discussion

The findings of this study showed high incidence rate of CLABSI (22.48 infections per 1000 catheter-days) among ICU patients in Greece, while the CLABSI rate in intensive care units (ICUs) in the United States is estimated to be 0.96 per 1000 central line days (Furuya et al. 2016). The main reason for the higher rates in our

Table 2 Univariate analysis between CLABSI and no CLABSI group

	Variables	CLABSI	No CLABSI	P
Diagnosis	Respiratory	74 (60.6%)	298 (49.7%)	0.018
	Infection	16 (13.1%)	52 (8.7%)	
BMI	BMI	26.5 ± 4.3	25.4 ± 4.5	
	Overweight and obese	92 (78.7%)	294 (49%)	
Comorbidity	Diabetes mellitus	28 (22.9%)	116 (19.3%)	0.034
CVC site	Jugular vein	62 (50.8%)	388 (64.7%)	
	Subclavian vein	32 (26.2%)	152 (25.3%)	0.001
	Femoral vein	28 (23%)	60 (10%)	
CVC type	Antimicrobial	92 (75.4%)	544 (90.7%)	0.001
N attempts for catheterization		5.6 ± 3.6	2.9 ± 2.3	0.001
Doctor's experience, years		9.7 ± 5.1	12.3 ± 5.3	0.001
Catheterization duration, min		18.2 ± 16.1	10.5 ± 9.5	0.001
MODS		9.1 ± 3.8	7.1 ± 3.7	0.001
LOS ICU, days		26.4 ± 17.9	18 ± 11.1	0.001
Total LOS, days		31.8 ± 16.7	23.4 ± 11.3	0.001
Outcome	Survival	32 (26.2%)	284 (47.3%)	0.001
Outcome, 28	Discharge	8 (6.6%)	196 (32.6%)	
Days	Died	54 (44.3%)	202 (33.7%)	0.001
	Stay in hospital/ICU	60 (49.1%)	202 (33.7%)	

CVC Central Venous Catheter, *ICU* Intensive Care Unit, *LOS* Length of Stay

Table 3 Predictor of CLABSI among all patients

Variable	B	P	OR	95% CI interval for B
BMI	0.201	0.001	1.223	1.107–1.351
Comorbidity, diabetes mellitus	−1.339	0.013	0.262	0.091–0.751
Doctors' experience	0.196	0.001	1.216	1.115–1.326
Type of catheter, antimicrobial	4.117	0.001	61.387	7.837–480.848
CVC site	−0.998	0.001	0.368	0.219–0.621
N attempts for CVC insertion	−0.185	0.009	0.831	0.724–0.954
Catheterization's duration	−0.042	0.001	0.959	0.936–0.983
MODS	−0.218	0.001	0.804	0.712–0.909

study may be due to doctors' low experience inducting the CVC and the nonuse of Ultrasound during the procedure.

Furthermore, this study showed that among the CLABSI and no CLABSI groups there is statistically significant difference concerning the diagnosis, BMI, comorbidity, CVC site, CVC type, N attempts for catheterization, doctors' experience, catheterization duration, MODS score, LOS ICU, total LOS as well as the outcome and 28 days' outcomes. According to the multivariate binary regression model, CLABSI was significantly predicted by the BMI ($p = 0.001$), by the diabetes mellitus as comorbidity ($p = 0.013$), by the doctors' experience ($p = 0.001$), by the type of CVC ($p = 0.001$), CVC site ($p = 0.001$), by the

number of efforts for CVC insertion ($p = 0.009$), by the catheterization's duration ($p = 0.001$) and by the MODS score ($p = 0.001$). In literature, there is a lack of studies relating obesity and the development of central venous catheter infections.

Pepin et al. (2015) conducted a retrospective longitudinal study of ICU patients, aged 18 years and older, who had central venous catheters. They found that the number of central line days was a predictor of CLABSI, consistent with the findings of our study. Lissauer et al. (2012), over a period of 2 years, studied critically ill surgical patients admitted to the intensive care unit (ICU) for ≥4 days. According to their findings, patients who developed CLABSI were (i) more likely to be male, (ii) more critically ill on ICU admission, (iii) more likely admitted to the emergency surgery service, and (iv) they had an association with reopening of recent laparotomy. The sample of said study consisted of surgical patients only, while the sample of our study consists of general patients in the ICU.

Tao et al. (2015) evaluated the efficacy of the topical administration, among others, of mupirocin in CVC care to prevent CLABSI in patients with major burns. They found that administering mupirocin, increasing the frequency of insertion-site care and avoiding cannulation at the burn site, reduced skin colonization at the CVC insertion site. Topical administration of mupirocin significantly reduced both the bacterial colonization rate at CVC tips and the incidence of CLABSI. In our study, we did not examine the correlation of similar factors affecting the prevention of CLABSI.

Dahan et al. (2016) conducted a retrospective matched case–control study of infants admitted to the neonatal ICUs of two hospitals in Canada. They found that active intraabdominal pathology, abdominal surgery in the prior 7 days, male sex, and ≥3 heel punctures were related to CLABSI. According to a multivariate matched analysis, intraabdominal pathology, and ≥3 heel punctures remained independent risk factors for CLABSI. Their findings cannot be compared with the findings of our study because of the different population characteristics (infants vs. adults).

Kaye et al. (2014) tried to quantify the impact of nosocomial bloodstream infections (BSI) on older patients, including mortality, length of stay (LOS), and costs attributed to BSI. They found that Nosocomial BSI in older adults was significantly associated with increases in 90-day mortality, increased LOS, and increased costs of care. Although the general conclusions of their study were similar with ours, we must point out that their sample did not consist of ICU patients.

4.1 Limitations

The limitations of the present study are the small number of the patients' sample and the fact that the study was conducted in the ICUs of only two hospitals.

5 Conclusions

CLABSI rates seem to be higher in Greece in comparison to other countries. Better staff training focused on care bundles preventing infections, better medical training focused on less efforts for CVC insertion, and use of Ultrasounds during the CVC insertion may be the main factors that can lead to lower CLABSI rates in obese patients. Finally, further research relating CLABSI rates in ICU patients and obesity is needed.

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Number of Brain States in an N-Body Dynamical Scenario According to the Universal Bekenstein Entropy Bound

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1 Introduction

The human brain is a complex, creative information-processing system. It is a well-known fact that the brain operates with extremely complicated processing capacity. This is achievable with the help of 100 billion neurons that the brain contains as well as the several hundred trillion synaptic connections that can process and exchange an amazing amount of information over the brain's neural network in a matter of milliseconds. This is possible due to the fact that the brain uses a parallel computing operation with the help of which our visual system can actually decode various complicated images in a 100 ms time. Over our lifetime the brain has the ability to store 10^9 bits of information, which is more than 50,000 times the text contained in the US Library of Congress (Neumann 2012).

As technology advanced from primitive to modern, the mechanisms used in today's science to describe the brain are also advancing rapidly. The basic idea of the information-processing theory is that the human mind is like a computer or information processor when compared to the theories put forward by behavioral scientists that people primarily respond to various stimuli. These theories equate thought-mechanisms to that of a computer, that receive and input and after various processes take place, deliver and output. Information is gathered from the senses

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(input), is stored and processed by the brain, which finally results in a behavioral response (output). Information-processing theories have been improved and broadened over the years.

In information-processing models, the so-called stage theory (Atkinson and Shiffrin 1968), which presents a sequential method, of input-processing-output (Craik and Lockhart 1972), is also noteworthy. Though influential, the linearity of this theory reduced the complexity of the human brain, and thus various theories were developed to further assess the inherent processes. Following this line of thought, Craik and Lockhart (ibid 1972) issued the "level of processing" model. The authors emphasized that information is processed in various ways, that is, perception, attention, labeling, and meaning, which eventually affect the ability to access the information later. In other words, the degree to which the information was elaborated upon, will affect how well the information was learned.

Next, Bransford broadened this idea by adding that information will be more easily retrieved if the way it is accessed is like the way in which it was stored (Morris et al. 1977). Therefore, the next major development in information-processing theory was the connectionist model, developed by Rumelhart and McClelland (1988). This model is supported by today's neuroscience research. It simply states that information that is stored simultaneously in different areas of the brain is connected as a network. The amount of connections a single piece of information has, will affect the ease of retrieval.

The general model of information-processing theory includes three components: (a) Sensory memory: In sensory memory, information is gathered via the senses through a process called transduction. Through receptor cell activity, it is altered into a form of information that the brain could process. These memories, usually unconscious, last for a very short amount of time, ranging up to 3 s. Our senses are constantly bombarded with huge amounts of information. Our sensory memory acts as a filter, by focusing on what is important, and forgetting what is unnecessary. Sensory information catches our attention, and progresses into working memory, only if it is seen as relevant or is familiar. (b) Working memory and short-term memory: It was Baddeley (2001) who issued a model of working memory that consisted of three components. The executive controls system oversees all working memory activity, including selection of information, method of processing, meaning, and finally deciding whether to transfer it to long-term memory or forget it. Two counterparts of this system are the auditory loop, where auditory information is processed, and the visual-spatial check pad, where visual information is processed. Sensory memories transferred into working memory will last for 15–20 s, with a capacity for 5–9 pieces or chunks of information. Information is maintained in working memory through maintenance or elaborative rehearsal. Maintenance refers to repetition, while elaboration refers to the organization of information (such as chunking or chronology). The processing that occurs in working memory is affected by several factors. Firstly, individuals have varying levels of cognitive load and the amount of mental effort they can engage in at a given moment differs, due to individual characteristics and intellectual capacities. Secondly, information that has been repeated many times becomes automatic and thus does not require much

cognitive resources (e.g., driving a car or operating a computer). Lastly, according to the task at hand, individuals use selective processing to focus on information that is highly relevant and necessary. Finally: (c) Long-term memory: Long-term memory includes various types of information: declarative (semantic and episodic), procedural (how to do something), and imagery (mental images). As opposed to the previous memory constructs, long-term memory has unlimited space. The crucial factor of long-term memory is how well organized the information is. This is affected by proper encoding (elaboration processes in transferring to long-term memory) and retrieval processes (scanning memory for information and transferring it into working memory so that it could be used).

As emphasized in Bransford's work, the degree of similarity between the way information was encoded and the way it is being accessed will shape the quality of the retrieval processes. In general, we remember a lot less information than the information stored there. Finally, to conclude we say that the human capacity for information processing is limited, that is, the amount of information retained in the working memory is limited. Therefore, when we try to perform several different tasks at the same time, the corresponding performance deteriorates. The neurophysiological basis of this phenomenon is to a large degree unknown.

In this chapter, our approach is to use a well-known, established law of physics that puts boundaries in entropy and therefore information. This is the well-known Bekenstein bound, which predicts how much information somebody needs to completely describe this particular physical system, the brain, down to its tiniest detail.

2 The Theory of the Bekenstein Bound

In this chapter, our focus of interest is the brain; therefore, we consider the brain to be our physical system of interest, of finite physical dimensions. The main idea will be to use Bekenstein's bound in the estimation of entropy S and from that, for the estimation of information N in bits. This is an upper limit of the entropy S or information N contained within a given finite region of space, of finite amount of energy content E that corresponds to a total amount of mass m. The Bekenstein bound can also be thought as the maximum amount of information required to completely describe a given physical system down to the tiniest quantum level. Thus, the Bekenstein bound for the entropy S can be written in the following way:

$$S_B \leq \frac{2\pi k_B ER}{\hbar c} \leq \frac{2\pi c k_B mR}{\hbar} \tag{1}$$

where S is the entropy, k_B is the Boltzmann constant, R is the radius of a sphere that can enclose the given system, $E = mc^2$ is the total mass–energy including any rest masses (in our case the mass of the brain, which is equal to $E_b = mbc^2$), $\hbar$ is the reduced Planck constant, and c is the speed of light. Note that Eq. (1) does not

contain the gravitational constant G, in spite the fact that gravity is a very important force in every physical system.

On the other hand, given the number of the information N in bits, the entropy of a physical system (Haranas and Gkigkitzis 2013) can be written in the following way:

$$S = 1.443 N k_B \ln 2, \tag{2}$$

where k_B is the Boltzmann constant, and the constant 1.443 comes from the fact that 1nat = 1/ln2 bits since ln2 is usually related to the information unit of nat. Next, the equation we solve for the number of information N in bits that the brain requires to describe the brain down to its tiniest detail is given by

$$N \geq \frac{2\pi c m_b R_b}{1.443 \ln 2 \hbar} \geq \frac{6.282 c m_b R_b}{\hbar}. \tag{3}$$

With reference to Haranas et al. (2016), the term $cm_b R_b$ has units of kg m^2 s^{-1}. Thus, we conclude that this term might represent some form of action, which reads:

$$\hbar_b = c m_b R_b. \tag{4}$$

Let us attempt to define this term as a brain quantum of action h_b. Using the following values for the mass of the male and female brains, that is, m_b = 1.3 kg, female m_b = 1.5 kg (to a spherical approximation, Shoshani et al. 2006), and using a brain volume $V_b = 1350\,\text{cm}^3$ (Cosgrove et al. 2007) we find that $R_b = 0.0686$ m. Substituting, using in Eq. (4) we obtain a first estimate for the brain quantum of action h_n to be:

$$\hbar_{b_{\text{female}}} = c m_b R_b = 2.675 \times 10^7\,\text{Js}, \tag{5}$$

$$\hbar_{b_{\text{male}}} = c m_b R_b = 3.087 \times 10^7\,\text{Js} \tag{6}$$

Considering equations (5) and (6), we define a corresponding Compton wavelength in the brain λ_C that is equal to:

$$\lambda_{C_{\text{male}}} = \frac{\hbar_b}{m_b c} = 0.0686\,\text{m}, \tag{7}$$

$$\lambda_{C_{\text{fem}}} = \frac{\hbar_{b_{\text{fem}}}}{m_{b_{\text{fem}}} c} \cong 0.0686\,\text{m}. \tag{8}$$

In principle, if the physical dimension of an object becomes equal to the Compton wavelength, quantum effects are predominant. But if quantum effects are present in the operation of the brain at some level, we would expect

$h_b = h/2\pi$ in some way to be related to Planck's h. Using Eq. (3), we can write:

$$N \geq 6.282\left(\frac{\hbar_b}{\hbar}\right), \tag{9}$$

From which we find that

$$\hbar_b \text{ " } 0.159N\hbar. \tag{10}$$

Thus, for specific values of the information bit number N, Eq. (10) predicts a brain action constant h_b that is quantized in units of the Planck constant h, if the product becomes an integer multiple of the Planck's constant h. This is possible if the number of information N takes values N = 1/0.159, 2/0.159, 3/0.159….n/0.159. Substituting Eq. (10) in (7) and (8) we obtain:

$$\lambda_{\text{male}} = \frac{0.159N}{m_{B_{\text{male}}}c}\hbar, \tag{11}$$

$$\lambda_{\text{fem}} = \frac{0.159N}{m_{B_{\text{fem}}}c}\hbar. \tag{12}$$

For quantization of the Compton length in units of h we then must integer values of $\frac{mBc}{0.159} = n$, where n = 1, 2, …..k.

3 The Number of States of the Human Brain

If N is the number of information bit for the brain, then the corresponding number of states of the brain is equal to

$$\Omega_b = 2^N. \tag{13}$$

Therefore, using Eq. (9) we find that

$$\Omega_b = 2^{6.282\left(\frac{\hbar_b}{\hbar}\right)}, \tag{14}$$

which is a constant, since all the parameters on the exponent are just constants for both male and female brains. We can also derive a different expression for the number of states in the brain, as a function of brain temperature and neuron correlation parameter b. With reference to Haranas and Gkigkitzis (2013), we can write the correlation coefficient b as

$$b = \frac{1}{3}T^{3/2}W\left[\frac{3}{T^{3/2}}e^{-\frac{2\pi c k_B m_b R_b}{\hbar T^{3/2}}}\right] = \frac{1}{3}T^{3/2}W\left[\frac{3}{T^{3/2}}e^{\frac{-S_B}{T^{3/2}}}\right], \tag{15}$$

where S_B is the Bekenstein bound entropy of the brain as a physical system. Substituting, using Eq. (2) we can write the correlation coefficient $\boldsymbol{b}$ as a function of information:

$$b = \frac{1}{3}T^{3/2}W\left[\frac{3}{T^{3/2}}e^{-\frac{1.443 k_B \ln 2N}{T^{3/2}}}\right], \tag{16}$$

Therefore, we can relate the number of information to the correlation parameter between two neurons, which takes the form:

$$N = -\frac{1.00677}{k_B}T^{3/2}W\left[be^{\frac{3b}{T^{3/2}}}\right]. \tag{17}$$

Using Eq. (17), Eq. (13) can be rewritten as

$$\Omega_b = 2^{-\frac{1.00677}{k_B}T^{3/2}\ln\left[be^{\frac{3b}{T^{3/2}}}\right]}. \tag{18}$$

Usually, the correlation coefficient b lies in the limits $0 \leq b \leq 1$, making the number of states omega positive.

4 Neuron Correlation Parameter and Its Relation to Neuron Potential and Kinetic Energy

With reference to Saslaw (1987), Eq. (16) for the correlation coefficient between a pair of neurons in an N body will be equal to the ratio of potential energy U to that of the kinetic energy K of the two neurons, given by

$$b = -\frac{U}{2K}, \tag{19}$$

therefore, Eq. (16) can be written in the following way:

$$-\frac{U}{2K} = \frac{1}{3}T^{3/2}W\left[\frac{3}{T^{3/2}}e^{-\frac{1.443 k_B \ln 2N}{T^{3/2}}}\right]. \tag{20}$$

It is conceptually challenging to define the kinetic energy for a pair of neurons, since it is not clear if neurons move or not and in what way. We know that neurons have mass, but in what way can we define neuron velocity? We define the potential energy between a pair of neurons as

$$U = -\frac{Gm_n m_n}{r_n} = -\frac{Gm_n^2}{\left(1/\sqrt{n_n}\right)}, \tag{21}$$

where, m_n is the mass of the neuron, and the average distance between a pair of neurons in an N body scenario can be equal to $r_n = \overline{r} = \frac{1}{\sqrt{n}}$ (Saslaw 1987), where n is the average number density of neurons/m^3 when considering the brain to be an infinite thermodynamically homogeneous system, with respect to the size of the neurons. Therefore, we derive the kinetic energy of a pair of neurons having temperature T and carrying N information bits to be

$$K = \frac{1}{2} m_n \dot{r}^2(t) = \frac{3Gm_n^2\sqrt{n}}{2T^{3/2} W\left[\frac{3}{T^{3/2}} e^{-\frac{0.99328 k_B N}{T^{3/2}}}\right]}, \tag{22}$$

where, W is the Lambert function of the indicated argument. As for the kinetic energy and the term r dot in Eq. (22), we can say that this particular time derivative of the distance $r(t)$ between two neurons indicates the expression of kinetic energy for the system of two neurons in a nonconventional phase space, where the distance changes as dynamic function of information, temperature, mass, and time, with certain proportionality constants such as G and k_B (an example would be the analysis in Eq. (27)). Such an interpretation would, of course, go beyond the standard space-time coordinates x, y, z, t (where everything looks immobile as it is the case with neuronal networks in a human brain) and it would involve other independent variables such as temperature and information, that may have a biophysical origin. For example, information transfer between two neurons may be a determining factor stating that two neurons are "near each other" or "away from each other." Therefore, the time rate of $r(t)$ might represent the velocity at which a pair of neurons approach or recede from each other upon experiencing a transfer of N number of information bits.

5 Discussion and Numerical Results

Taking the temperature of the brain to be T_b =36.9 C = 310.06 K (Wang et al. 2014) we obtain the following numerical expression, for all the possible number brain states, as a function of the number of information bits N transmitted through the neurons:

Table 1 Tabulated results of number of information N and also the corresponding brain states Ω_b for three corresponding brain temperatures and three corresponding neuron correlation parameters b

Absolute brain temperature T_b [K]	Neuron correlation coefficient b_n	Number of information N [bits]	Brain number of states $\Omega_b = 2^N$
308.25	0.999446	5.245×10^{19}	$2^{5.24542\times10^{16}} = 10^{1.578902327\times10^{19}}$
309.75	0.999450	5.883×10^{19}	$2^{\left(5.8337\times10^{19}\right)} = 10^{1.756118682\times10^{19}}$
310.85	0.999453	2.458×10^{19}	$2^{\left(2.458\times10^{19}\right)} = 10^{0.739931727\times10^{19}}$

Looking at Table 1 we say that the amount of information bits N has been calculated using Eq. (17), considering the theory of an N-body galactic dynamics scenario it is reduced but still a very large number. We find that the higher number of states between three different temperatures occurs at the temperature $T = 309.75$ K or $T = 36.6$ C. At this point, to approximate the number of states omega in Table 1 we try a series expansion of the form:

$$\Omega_b = 2^N \cong 1 + N\ln 2 + \frac{N^2}{2}\ln 2^2 + \frac{N^3}{6}\ln 2^3 + \frac{N^4}{24}\ln 2^4 + \ldots\ldots, \tag{23}$$

From Eq. (23) we see that the series diverge and different orders of expansion result in brain state numbers that significantly vary. For example, a first-order expansion results in $\Omega_b = 3.635 \times 10^{19}$ states where keeping up to second order we obtain $\Omega_b = 6.608 \times 10^{38}$ states and an inclusion of a third-order term increases omega to $b = 8.008 \times 10^{57}$ states, where an eighth-order expansion will result in a huge number of states of the order of $\Omega_b = 10^{151}$, which magnitude wise is a number larger than the total number of information bits in the universe. Therefore, it is easily understood that a series expansion of the number 2^N cannot calculate the numbers in the last column of Table 1 above. At this point, let us look at Eq. (16). Using the numerical values of Eqs (5) and (6), we obtain:

$$\Omega_{b_{\text{male}}} \leq 2^{6.282\left(\frac{2.765\times10^{7}}{1.054\times10^{-34}}\right)} \leq 2^{1.839\times10^{42}} \leq 10^{5.535941608\times10^{41}} \text{ states}, \tag{24}$$

$$\Omega_{b_{\text{fem}}} \leq 2^{6.282\left(\frac{2.675\times10^{7}}{1.054\times10^{-34}}\right)} \leq 2^{1.594\times10^{42}} \leq 10^{4.79841812\times10^{41}} \text{ states}. \tag{25}$$

Equations (24) and (25) are the maximum number of states that the male and female brain can have respectively, as predicted using the universal Bekenstein bound of entropy. In Fig. 1, we plot the number of information N in bits between a pair of brain neurons as a function of their correlation parameter b. We find that as the correlation parameter increases, the number of information bits decreases in an almost negative exponential graph. Similarly, in Fig. 2 we plot the number of information

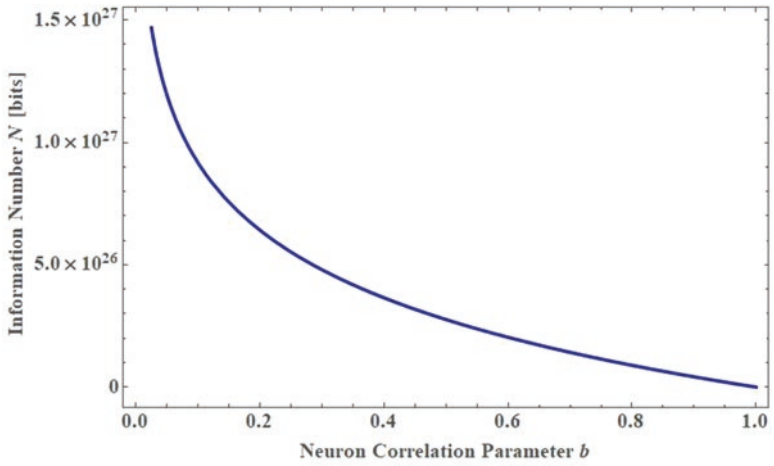

Fig. 1 Plot of the number of information N in bits between a pair of brain neurons as a function of the correlation parameter b between the two neurons

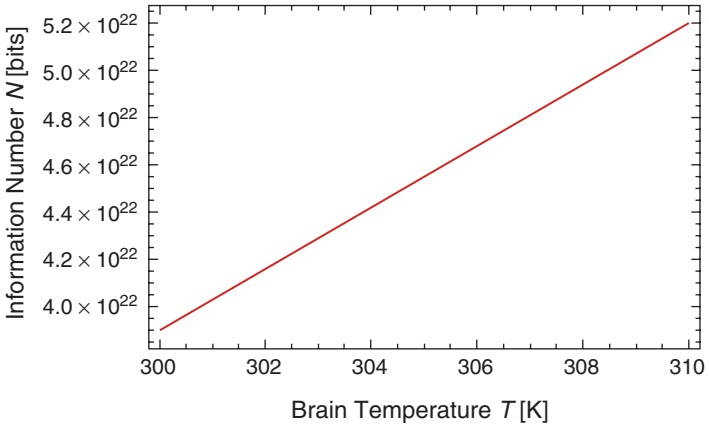

Fig. 2 Plot of the number of information N in bits between a pair of brain neurons as a function of brain temperature T

N in bits between a pair of brain neurons as a function of brain temperature T. In Table 2 we tabulate the number of information N in bits between two neurons as a function of brain temperature T and for a single correlation value parameter b. We find that at higher brain temperatures the required amount of information must increase for neurons to communicate. With reference to our conjecture that the time derivative of the displacement $r(t)$ is the distance between neurons in relation to the networks that they are moving, we derive the following solution for the radial displacement of the networks from the differential equation as it is given in Eq. (22), subjected to the following initial conditions, that is, $r(0) = 0$ and assuming that the number of information N is a generic function of time, that is, $N = N(t)$, we obtain

Table 2 Number of information N in bits as a function of brain temperature T for a single value of neuron correlation parameter $b = 0.9990000$

Brain temperature [K]	Brain temperature [C]	Number of information [bits]
300	26.85	3.898×10^{22}
301	27.85	4.027×10^{22}
302	28.85	4.157×10^{22}
303	29.85	4.286×10^{22}
304	30.85	4.416×10^{22}
305	31.85	4.545×10^{22}
306	32.85	4.675×10^{22}
307	33.85	4.806×10^{22}
308	34.85	4.936×10^{22}
309	35.85	5.067×10^{22}
310	36.85	5.198×10^{22}
311	37.85	5.329×10^{22}
312	38.85	5.460×10^{22}
313	39.85	5.723×10^{22}
314	40.85	5.855×10^{22}
315	41.85	5.978×10^{22}

$$r(t) = \pm \frac{2\sqrt{3Gm_n}}{\alpha k_B} n^{1/4} T^{3/4} \frac{\left[1 + \left(W\left(3T^{-3/2}\right) W\left(3T^{-3/2} e^{-\frac{\alpha k_B t}{T^{3/2}}}\right)\right)^{1/2}\right]\left[W\left(3T^{-3/2}\right) - W\left(3T^{-3/2} e^{-\frac{\alpha k_B t}{T^{3/2}}}\right)\right]}{\left(W\left(3T^{-3/2}\right) W\left(3T^{-3/2} e^{-\frac{\alpha k_B t}{T^{3/2}}}\right)\right)^{1/2}}. \quad (26)$$

In the case where the number of information in the neurons is constant, the solution becomes

$$r(t) = \pm \left[\frac{3Gm_n}{W\left(3T^{-3/2} e^{-\alpha k_B N T^{-3/2}}\right)}\right]^{1/2} n^{1/4} t. \quad (27)$$

Where the constants $\alpha = 0.99328$, k_B = Boltzmann's constant and W is the Lambert function of the indicated argument. In general, one might expect that brain temperature might be an analytical function of time and even distance with regard to a certain point of the brain, and therefore a much more elaborate solution could be obtained using Eq. (22). This is the focus of our current research.

Furthermore, it is possible that the human brain functions on the basis of a protocol that compresses incoming or self-generating information (and states) in a way that would require fewer physical resources due to its limitations. A similar processing scheme is shown in the study of Quantum Information Theory. Super-dense coding is a quantum communication protocol for the transmission of information from a sender to a receiver, by sending qubits (qutrits, qudits, etc., for higher-level quantum systems) under the assumption that they share an entangled state. Such a scheme is used to convey two bits of information, with certain quantum considerations and restrictions applying for more bits of information. Distributed quantum dense coding schemes (Bruss et al. 2004) and dense coding with multipartite quantum states have been studied before. This idea of dense coding can be thought of as a process of compressing states emitted by a quantum source of information, so that they require fewer physical resources to store qubits. Moreover, quantum logic gates operate on qubits and they are the building blocks of quantum circuits, very much like classical logic gates do for conventional digital circuits. Quantum logic gates are reversible, and it is possible to perform classical computing using only reversible gates (e.g., the reversible Toffoli gate that can implement all Boolean functions, using ancillary bits (memory)). Moreover, in the case of the human brain, one may expect the production of emergent properties and massive parallelism of interconnected networks of locally active components. This could possibly be due to designless networks of matter that exhibit robust computational functionality, utilizing whatever physical properties are exploitable. The coding scheme of the brain must meet the criteria for the physical realization of cellular neural networks, such as universality, compactness, robustness and evolvability. Evolvability implies scalability to perform more advanced tasks, such as capacitive crosstalk, in an energy-efficient way of computation, for solving problems that are very hard to tackle in conventional architectures. On the basis of these observations, the quantity h_b 0.159 may serve an information and/or state compression mechanism as a quantized proportionality channeling transformer that can reduce a vast amount of information from the order 10^{42} bits down to the order of 10^5 bits through super-dense coding.

For example, if we use Eq. (10) and $N \approx 10^{42}$ the maximum number of information in the brain according to the universal Bekenstein entropy bound we find that

$$\hbar_B = 0.159\left(10^{42}\right)\left(1.054\times10^{-34}\right) = 1.676\times10^{7}\,\mathrm{J\,s}. \tag{28}$$

These super-dense coding units operate as nonlinear interconnected transistors that can configure the architecture of Boolean-like logic gates. This would enable the link of sensory information to perception, recognition, and recollection. The aforementioned gates could be the carriers of designless networks that would allow the support of these attributes, as well as an optimization scheme that will turn on and off memory, in an effort to evaluate the significance of the input for application of appropriate behavior (Bose et al. 2005). Such an information transfer will allow the creation of accurate replicas of real-life events as a reconstructed present, with the

influence of emotions, motivation, and selective attention that introduce additional subjective biases (Mesulam 1998). "…the biological purpose of perceptual and mnemonic abilities is not necessarily to enhance representational fidelity but rather to optimize the adaptive value of the behaviors that are guided by the relevant perceptions and recollections."

6 Conclusions

Information theory is about where data are stored, how they can be moved, and how they can be accessed. The basic storage unit for information varies in each system and differs in descriptions. The concepts of information, entropy, entanglement, etc., are related to the speed and sensitivity of our senses and response systems to various stimuli, as well as the emergence that may operate at a level of nonseparability of different states. All the above are susceptible to external contamination through interaction with the environment. In computer science, the existence of the Bekenstein bound implies that there is a maximum information-processing rate (Bremermann's limit) for a physical system that has a finite size and energy, and that a Turing machine with finite physical dimensions and unbounded memory is not physically possible. Therefore, the brain is not a Turing machine. That means that the brain is not an algorithmic manipulator of intrinsically meaningless symbols such as bits. Of course, consciousness may involve hardware other than neurons. According to Godel's Theorem, any mathematical system of symbols and rules that is complex enough to encode operations of arithmetic, can either be consistent (no contradictions such as a statement that is false and true at the same time) or complete (all true and false statement can be proven to be true or false within the system) but never both (Friedman 2002). According to Casti (Five Golden Rules: Great Theories of twentieth-Century Mathematics—and Why They Matter, 1997), "By standing outside the incomplete, consistent formal system Godel's results imply that humans can know there exists some true, but unprovable statement. But the machine cannot prove this fact; hence, a human can beat every machine since such a true, but unprovable statement, exists, for every machine." However, the human consciousness knows the truth of such a Godel statement, while a computer would have to axiomatically prove the statement in its own formal system. This knowledge of the truth of the statement, that not even the human brain can prove in a formal system, may be tied up to meta-language and meta-proofs that go outside a brain-algorithmic logic system, such as the resolution of mathematical paradoxes (Friedman 2002). Unlike Turing machines, the human consciousness has some genuine randomness in irrational behavior, creativity, and language, which is thought to be a carryover of human genetic history, along with some algorithmic processes that the human brain controls, such as kidney regulation, the operation of pancreas, the immune response. Therefore, the brain may be only in part an organic computer as well as a meta-processor (Friedman 2002). Thus, the human mind may operate in a meta-level to be consistent and complete and overcome Godel's

constraint. However, it is believed that a Turing machine may be able to also do this meta-processing if someone reprograms the machine, which could possibly happen in an evolutionistic process.

In such a case, there would be no fundamental difference between a human brain (or human mind or human conscience) and a Turing machine (an advancing algorithmic manipulator), since the meta-processing of the one is met by the evolution of the other. However, if our results can be verified experimentally, they will support the idea that Bekenstein's bound is valid for the human brain, and the human brain is fundamentally different from a Turing machine. We conjecture that since no such difference seems to be present at the level of the formal logic systems and the meta-level (with the necessary condition that someone needs to reprogram a Turing machine), the difference may be in that consciousness is neither a consistent nor an inconsistent system (statements can be true and false at the same time, in a certain way), at all levels of complexity. This is something that will not be possible for a logical system of symbols and rules, complex enough to encode arithmetic.

Note: All authors have contributed to this chapter equally.

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Burden and Sleeping Disorders of Family Caregivers of Hemodialysis Patients with Chronic Kidney Disease-End Stage: A Cross-Sectional Study

George Intas, Vasiliki Rokana, Pantelis Stergiannis, Eleftheria Chalari, and Fotios Anagnostopoulos

1 Introduction

All chronic diseases that require moderate or wide-term adaptation of patients' lifestyle can also affect the quality of life of their families. Particular attention is paid to the investigation and evaluation of the quality of life of family caregivers, as their well-being affects the ability of patients to cope with the requirements of managing their illness (Zacharopoulou et al. 2015).

The burden of care is determined on the basis of the physical, emotional, economic, and social responsibilities of the individuals who provide it. Chronic illnesses with a high level of disability can dramatically affect not only the patient but also the main caregiver who supports him/her. Conversely, the behavior of the patient is a factor that can increase the stress and burden intensity experienced by the caregiver. In addition, the long-term care period increases the burden. Its effect often results in family conflicts and reduced social function for patients and their carers (Parks and Novielli 2000; Lim and Zebrack 2004; Mashayekhi et al. 2015).

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Chronic renal failure is a disease that affects normal, psychological, functional ability and causes changes in the lifestyle and independence of the patient and their family, mainly due to its long-term treatment. Moreover, it reduces the living standards, causes physical and psychological problems, as well as restrictions on recreational, social, and work activities. Caregivers often feel disappointed, isolated, and have feelings of frustration due to their lack of support, and their inadequate training (Mashayekhi et al. 2015).

Families of patients with chronic kidney disease (CKD) provide supportive care both within the home and the Renal Dialysis Unit (RDU). This can affect their mental health. The frequent hospitalization of patients and the effects of the symptoms of the disease often lead to the occurrence of depression and the decrease of the quality of life of caregivers. Consequently, assessing the situation and identifying the needs of caregivers is very important (Mashayekhi et al. 2015).

The caregiver's burden is a general term used to describe the physical, emotional, and financial cost of care provided. It is defined as the permanent difficulty, anxiety, and/or the negative experiences of the caregiver during the provision of care and includes subjective and objective parameters. The objective ones include changes and disturbances of everyday life due to the management of the patient's disease. The subjective parameters refer to the response or attitude of the caregiver toward his/her duties (Parks and Novielli 2000; Lim and Zebrack 2004).

Early recognition of caregiver problems plays a key role in promoting their mental health. Focusing on their emotional state by controlling and preventing problems such as depression, poor sleep quality, neglect of their own physical health, through effective interventions and the creation of a social support network, can improve the quality of life not only of caregivers, but also of the patients who are receiving their care.

2 Materials and Methods

2.1 Aim

The aim of this study was to investigate the burden and sleep disorders of caregivers of hemodialysis patients.

2.2 Study Design

This is a cross-sectional study.

2.3 Participants

The sample of the study consisted of 310 family caregivers (response rate = 79.5%), who had the primary and/or complete responsibility for the care of hemodialysis patients. Data collection took place from 5 November 2016 to 31 March 2017.

2.4 Tools

2.4.1 Quality of Sleep

The caregivers' sleep quality assessment was conducted using the Pittsburgh Sleep Quality Index (PSQI). PSQI includes 19 items and evaluates 7 dimensions of sleep (subjective sleep, sleep latency, sleep duration, habitual sleep efficiency, sleep disorders, use of sleeping medication, and daytime dysfunction). It has a diagnostic sensitivity of 89.6% and a specificity of 86.5% (Kappa = 0.75, $p < 0.001$) in terms of the ability to distinguish between "good" and "poor" sleep quality (Buysse et al. 1989). The PSQI has been translated and validated in the Greek language (Perantoni et al. 2012).

The assessment of the caregivers' burden was based on the Zarit Burden Interview. The scale consists of 22 items—statements regarding the feelings of the caregivers. The respondents answer each item on a 5-point Likert scale (0 = never, 4 = always). The scale scoring ranges from 0 to 88 (Papastavrou et al. 2006; Zarit et al. 1980). The Zarit Burden Interview has been translated and validated in the Greek language (Kalokairinou et al. 2006).

Also, the Center for Epidemiologic Studies-Depression (CES-D) was used to assess the degree of depression experienced by caregiver, by detecting depressive symptoms. It includes 20 items. Each one is scored from 0 to 3, reflecting the feelings/thoughts or symptoms experienced by the responder during the previous week. It has been translated and validated in the Greek language (Fountoulakis et al. 2001; Kutsopulu-Sofikiti et al. 2009). The combination of CES-D and Zarit Burden Interview highlights whether and to what extent caregivers have negative psychological symptoms that are interpreted by the emotional, social, and economic burden that is created by the care of the patient (Radloff 1977).

2.5 Statistical Analysis

The statistical analysis was carried out using IBM SPSS 21.0 statistical package. Descriptive statistics including frequencies and percentages were used to summarize participant demographic characteristics and responses. Pearson Correlation Coefficient was used to explore the linear relationship between the dimensions of quality of life

and sleep. The range of values of this coefficient varies between −1 and +1. Zero represents no correlation between two variables. Values 0.21–0.40 suggest small, 0.41–0.60 moderate, 0.61–0.80 strong and 0.81 very strong correlation.

3 Results

The demographics of the respondents are shown in Table 1.

Table 1 Socio-demographic data ($n = 310$)

Variables		*N*	%
Gender	Male	100	32.3
	Female	210	67.7
Age, years	21–40	50	16.1%
	41–60	130	41.9%
	61–75	110	35.5%
	76+	20	6.5%
Marital status	Unmarried	270	87.1
	Married	40	12.9
Education level	<6 years	110	35.5
	6–9 years	20	6.5
	9–12 years	90	29
	12–14 years	30	9.7
	University	50	16.1
	None	10	3.2
Income, euro/year	None	80	25.8
	≤6.000	90	29
	6.001–12.000	90	29
	≥12.001	50	16.1
Occupation	Specialized worker	10	3.2
	Freelance	60	19.4
	Farmer	30	9.7
	Private employee	50	16.1
	State employee	50	16.1
	None	110	35.5
Place of residence	Same house with the patient	240	77.4
	Same building with the patient	30	9.7
	Same neighborhood with the patient	10	3.2
	Different house and neighborhood with	30	9.7
	The patient		
Relative	Husband	180	58.1
	Daughter/son	90	29.1
	Sister/brother	30	9.7
	Other	10	3.2

3.1 Burden

Based on the total score on this scale, about half of respondents had little or no burden (45.2%), 25.8% of them had moderate to severe burden, 19.4% had mild to moderate burden, and 9.7% had severe burden. The average personal strain score and the average role strain score of responders was 11.6 ± 8.6 and 8.9 ± 6.5, respectively. Table 2 presents the caregiver's burden per dimension.

3.2 Depression

There were 80 (25.8%) caregivers in predisposition and risk of depression and/or depressive symptomatology, with total score ranging from 16 to 23. The caregivers belonging to the depression group were mostly women (87.5%), they lived in the same house with the patient (62.5%), they were spouses (75%), they cared for the patient for more than 4 years (62.5%), and had a family income of <6000 euros (75%).

3.3 Sleep

According to the PSQI, 160 (51.6%) responders had bad quality of sleep and 150 (48.4%) responders had poor quality of sleep. The average score of PSQI was 5.68 (with a cutoff limit of 5). Most of the responders did not receive any drugs to help them sleep (87.1%), while 3.2% received drugs less than 1 day per week and 9.7% more than 3 days per week. The components that were more strongly related to the overall degree of sleep quality were actual duration of sleep ($r = 0.775$, $p < 0.001$) and dysfunctions during the day ($r = 0.802$, $p < 0.001$). Table 3 presents Pearson correlation coefficients among total burden, personal strain, role strain, years of care, caregiver's age, total sleep quality, and depression.

Table 2 Total score of burden per dimension

Burden	Personal strain		Role strain	
	N	%	*N*	%
Little or no (0–20)	130	42	110	35.5
Mild to moderate (21–40)	50	16.1	70	22.6
Moderate to severe (41–60)	90	29	90	29
Severe (61–88)	40	12.9	40	12.9

Table 3 Pearson correlational analysis for caregiver's burden

	1	2	3	4	5	6	7
1. Total burden	1						
2. Personal strain	0.952	1					
	0.000						
3. Role strain	0.901	0.919	1				
	0.000	0.000					
4. Years of care	0.182	0.128	0.039	1			
	0.328	0.493	0.834				
5. Caregiver's age	0.226	0.240	0.263	0.171	1		
	0.222	0.193	0.154	0.358			
6. Sleep quality	0.881	0.742	0.239	0.119	0.462	1	
	0.000	0.000	0.131	0.227	0.249		
7. Depression	0.495	0.149	0.658	0.044	0.214	0.616	1
	0.005	0.317	0.000	0.819	0.117	0.000	

4 Discussion

We found that caregivers of hemodialysis patients have increased burden; 58.1% of the responders had moderate to very severe burden in the factor of personal strain, which interprets 44.4% of the fluctuation (Kalokairinou et al. 2006). While the role strain factor was found to be 64.5%, personal strain and role strain had strong correlations with the total burden ($r = 0.952$ and $r = 0.901$, respectively). The burden was not related to the age of the caregiver or the years of care. The results reinforce the findings of other surveys, but value comparisons are not attempted, as the way of dividing the burdens' dimensions varies from researcher to researcher.

A study in Saudi Arabia, analyzing the two basic dimensions (personal strain and role strain) presents findings similar to ours, in each dimension and in the overall score of caregivers' burden (Bayoumi 2014). Another study in Iran, using the Caregiver burden questionnaire, found severe and moderate burden in 49% of caregivers (Mashayekhi et al. 2015). Similarly, in India, 26/50 caregivers were found with serious and very serious burden (Jadhav et al. 2014). On the other hand, the findings in another study conducted in India in a sample of 100 caregivers, showed that the 86% of them had mild and moderate burden (Subhashini and Indira 2016). In all studies, the majority of caregivers were women and the relationship with the patient was that of spouses, similar to our study.

Moderate to severe probability of depressive disorder development was found in 26.7% of caregivers, while 20% of responders were predisposed to depression. Our results agree with studies of caregivers of chronically ill and hemodialysis patients (Shean and Baldwin 2008; Suri et al. 2011). The degree of depression risk is strongly related to sleep quality ($r = 0.616$) and moderately related to total burden ($r = 0.495$).

We found that most caregivers had poor sleep quality. In agreement with the results of our study, a study in Turkey using PSQI found that caregivers of

hemodialysis patients had poor sleep quality as well as high rates of anxiety and depression (Avşar et al. 2015). Also in Turkey, another study evaluated sleep quality, anxiety, and depression in 142 hemodialysis patients and their caregivers using PSQI and HADS and found that caregivers had poor sleep quality (overall score 11.9 ± 3.0) and high levels of depression (Celik et al. 2012).

In Pakistan, one-third of caregivers of hemodialysis patients, assessed using Beck's Depression Inventory, were found with moderate and severe depression. The major risk factors for depression were marital status and unemployment (Ahmad et al. 2012). The combination of decreased sleep quality and depressive symptoms enhances and may interpret the burden experienced and reported by caregivers of hemodialysis patients.

4.1 Limitations

A limitation of the study is the prevalence of marital status among caregivers and the fact that ethnicity in both groups was limited to Greek, thus preventing the investigation of correlations between various research parameters and especially demographic and personal data relating to similar research in literature.

5 Conclusions

The evolution of biomedical technology and medical science has greatly improved the life expectancy of patients with CKD and their clinical symptoms. At the same time, this improvement has positive effects on the social support and interaction of patients and their families. The requirements and obligations of the dialysis procedure affect the quality of life and the mental and physical health of caregivers of hemodialysis patients and their families.

Continuous and regular assessment of the caregivers' quality of life and the provision of psychological support will reduce the burden of caregivers and improve the emotional disorders they face.

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Quality of Life in Type 2 Diabetes Mellitus Patients with Neuropsychological Deficits

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1 Introduction

Diabetes mellitus (DM) is a common metabolic disorder that has escalated as an important global health concern with significant worldwide increase in prevalence rates and projections for higher future rates (Wild et al. 2004). Although DM can lead to life-threatening renal and cardiovascular complications, effective modulations of these disorders may allow the diabetic patient to achieve normal life expectancy and quality of life (Biessels et al. 2008). Both type 1 and type 2 diabetic patients are characterized by poor glycemic control with a differential comorbidity pattern and pathophysiological mechanisms. Type1 diabetes mellitus (T1DM) is an autoimmune disorder with destruction of the pancreatic cells that leads to insulin deficiency. It encompasses approximately 5–10% of the diabetic clinical cases and age of onset is usually during childhood or early adulthood. Type 2 diabetes mellitus (T2DM) is pathophysiologically related to insulin insensitivity and insulin resistance (IR) leading to progressive β-cell pancreatic dysfunction (Awad et al. 2004; Arvanitakis et al. 2004; Brands et al. 2007). Older age and male gender are considered significantly predisposed for developing diabetes (Biessels et al. 2008).

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Although the somatic implications of DM are well established, evidence in the literature suggests that diabetic patients are also at risk to develop cognitive dysfunctions (Awad et al. 2004; Lee et al. 2014). Despite the many similarities of cognitive dysfunctions amongst T1DM and T2DM patients, the pattern and severity of cognitive impairment may differ in some respects (McCrimmon et al. 2012). Most type 2 diabetic patients often have deficits on standardized neuropsychological measures of learning and episodic memory, which is less prevalent in type 1 patients. Another important feature of cognitively impaired T2DM patients is that their relative risk for developing mild cognitive impairment and their accelerated progress to dementia is significantly increased compared to the general population (Lee et al. 2014; Whitmer 2007). On the contrary, T1DM patients show reduced general intelligence, which is rarely seen in people with type 2 diabetes (McCrimmon et al. 2012; Koekhoek et al. 2015). On the other hand, both diabetic groups have deficits in mental information processing speed, attention, and executive function (Koekhoek et al. 2015). In terms of brain alterations in this population, studies utilizing neuroimaging and other neuroscientific techniques have reported that both diabetic types show neural slowing, increased cortical atrophy, microstructural abnormalities in the white matter tracts, and altered structural and functional connectivity (McCrimmon et al. 2012).

As mentioned previously, T2DM is associated with deficits across multiple domains of cognition with deficits in episodic memory, mental information processing speed, and executive functions being the most frequent and robust findings. Language and semantic memory, on the other hand, remain relatively unaffected (Koekhoek et al. 2015). More disturbing, however, is the fact that cognitive domains impaired in T2DM appear to also be impaired in prediabetic stages, although to a less severe extent, possibly associated with glucose intolerance (Lee et al. 2014). Although it is evident from several studies that cognitive functions are impaired in type 2 diabetics, the mechanism that involves multiple factors, including genetic predisposition, glycemic control (recurrent hypoglycemia and hyperglycemia) (Mansur et al. 2018), microvascular disease, functional brain insulin deficiency, HPA axis dysregulation, obesity, hypertension, amyloid deposition, and other factors is still unclear (Lee et al. 2014; Reijmer et al. 2010).

Furthermore, evidence from recent studies has indicated a close pathophysiological relationship and pathogenetic mechanism between Alzheimer's disease (AD) and (T2DM) patients. This includes factors such as impaired insulin signaling, insulin resistance, advanced protein glycation, and oxidative stress. Moreover, T2DM and AD patients have similar amyloid beta deposits both in the pancreas and the brain. As a result, several researchers have proposed AD to be a Type 3 DM (Biessels et al. 2006; Cukierman et al. 2005).

As a chronic disease, T2DM may have a significant negative impact on quality of life, activities of daily living and employment status (AI Hayek et al. 2014; Vaatainen et al. 2014; Zurita-Cruz et al. 2018). It is generally accepted that diabetic patients experience a serious decline in general quality of life (QOL) mainly influencing health-related quality of life (HR QOL) on a worldwide scale, with variability only on the grade of influence (Lu et al. 2017; Trikkalinou et al. 2017). The impact of

type 2 DM on QOL was highlighted by (Prassana Kumar et al. 2018) who found that the most affected life domain was the freedom of their patients to eat. Positive associations between QOL and gender, age, education, duration of disease, HbA1c, insulin treatment, and comorbidities were also established. In a cross-sectional survey it was noted that high mortality rate, economic status, complications associated with (T2DM), longer duration of diabetes, and poor general health were independent risk factors for quality of life among diabetic patients (AI Hayek et al. 2014). More recently, (Zurita-Cruz et al. 2018) a cross-sectional study reported that (T2DM) patients' global health-related quality of life (global HRQOL) was negatively influenced by older age, female gender, occupation, comorbidities, and duration of diabetes.

Regarding the association between cognitive impairment and QOL in type 2 diabetics, the literature is extremely limited, and many questions remain unanswered. In one of the few studies that have been conducted (Aithal et al. 2018) utilizing the WHOQOL-BREF questionnaire, the authors reported that QOL was decreased in their elderly diabetic patients with mild cognitive impairment (MCI), with most affected domains reflecting psychological and social relationships. Furthermore, an interesting study (Koekhoek et al. 2015) found that undiagnosed cognitive dysfunction in type 2 diabetics was associated with a poorer health status. With this finding in mind the authors suggested that T2DM patients with cognitive impairment are a vulnerable patient group that could benefit from treatment and care tailored to their special needs. Moreover, (Ojo and Brooke 2015) reports show that the self-management of diabetes is significantly affected by cognitive dysfunction, highlighting the need for detecting cognitive decline in this population in order to apply structured education strategies and lifestyle changes. Interestingly, a recent study found improved cognitive performance following physical activity in their type 2 diabetics, underscoring the need to apply such physical training interventions as early on as possible, even from the prediabetic stages (Podoski et al. 2017). The treatment of cognitive impairment in T2DM patients, however, remains a major concern, as the most recent Cochrane review on this issue found poor evidence that any specific treatment or treatment strategy can prevent or delay cognitive dysfunction in this population. Only intensive and standard glycemic control strategies provided moderate results regarding their efficacy on global cognitive functioning over a period of 40–60 months (Areosa Sastre et al. 2017).

What is evident from reviewing the literature on this issue is the scarcity of studies exploring cognitive impairment and associated QOL in type 2 diabetics. Moreover, considering that cognitively undiagnosed people with type 2 diabetes have poorer health status and that patients in this population with MCI were found to have lower levels of HRQOL, in the present study we aim to further the investigation regarding the cognitive performance of type 2 diabetes mellitus patients and the HRQOL of patients with neuropsychological deficits.

In this respect we hypothesized that: (a) patients diagnosed with type 2 diabetes mellitus are anticipated to present quantitatively poorer cognitive function compared to demographically matched healthy participants and (b) type 2 diabetes

mellitus patients formally diagnosed, by cognitive tests, with neuropsychological deficits are expected to have lower levels of HRQOL.

2 Methodology

2.1 Participants

Forty-four patients diagnosed with Type 2 Diabetes Mellitus (T2DM) and 28 healthy participants took part in the present study. Individuals with T2DM were recruited from the outpatient endocrinology units of the Laiko Hospital in Athens, and from the University General Hospital of Patras, in Patras, Greece. Patients were included after having been diagnosed with T2DM by an experienced diabetes specialist endocrinologist/pathologist, according to internationally recognized criteria (see 3). The criteria for participation for both patients and healthy controls were to (1) have no history of major psychiatric disorders such as schizophrenia and bipolar disorder, or neurological disorders such as stroke, epilepsy, encephalitis, or severe traumatic brain injury; (2) have no dementia, and their score on the Mini Mental State Examination (MMSE) to be greater than or equal to 24; (3) be native speakers of Greek; (4) be between 35 and 60 years of age, and (5) have normal or corrected vision and hearing. Written consent was obtained from all participants after having been informed of the nature of the study they would take part in. The research protocol was approved by the Ethics Committee of the University General Hospital of Patras. Table 1 presents the demographic and clinical characteristics of all participants and Table 2 the clinical characteristics of the diabetic patients.

Table 1 Demographic and clinical characteristics of the two groups mean: (SD)

Variable	T2DM $N = 44$	CG $N = 28$
Gender (male)	35	16
Age (in years)	54.55 (13.35)	59.23 (7.45)
Years of Education	11.61 (3.73)	12.64 (4.10)
MMSE	28.14 (1.82)	29.11 (1.94)
WASI Vocabulary Scale T-score	44.7	45.6
BDI-FS	4.14 (2.31)	1.93 (1.30)

T2DM Type 2 Diabetes Mellitus, *CG* Healthy control group, *MMSE* Mini Mental State Examination, *WASI* Wechsler Abbreviated Scale of Intelligence, *BDI-FS* Beck Depression Inventory-Fast Screen

Note: Premorbid intelligence level was estimated by administering the vocabulary subscale of the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler 1999), Greek adapted version (Messinis and Papathanasopoulos 2009)

Table 2 Clinical characteristics of diabetic patients

Characteristic	Mean (Standard deviation)
Disease duration	6.5 (2.3)
Body Mass Index	30.08 (5.86)
HbA1C	8.78 (6.87)
Hypoglycemic episodes per month	4.90 (12.05)
Smokers (%)	22.9
Employed (%)	18.2
Systolic blood pressure	140.2 (18.00)
Diastolic blood pressure	82 (10.00)

2.2 Neuropsychological Assessment

All participants underwent a comprehensive battery of neuropsychological tests, translated and adapted to the Greek language. They were conducted by trained clinicians under the supervision of a clinical neuropsychologist. According to the literature, these tests are sensitive to cognitive deficits experienced by patients with T2DM (Palta et al. 2014). The functions assessed and the tests administered are described below.

2.2.1 General Mental State

For the assessment of the general mental state, the Mini Mental State Examination (MMSE) was administrated. The MMSE evaluates memory, attention, orientation, visuospatial and language skills. Although the MMSE is useful as a screening test, it is not sensitive to subtle cognitive deficits in various domains and does not assess executive dysfunction (Folstein et al. 1975). A validation study of the MMSE in the Greek population was conducted by (Fountoulakis et al. 2000).

2.2.2 Estimated Premorbid Intelligence

The WASI was developed by (Wechsler 1999) for the estimation of general intellectual ability. The WASI consists of four subtests: Vocabulary, Similarities, Block Design, and Matrix Reasoning. The estimation of the Full-Scale Intelligence Quotient can be obtained from the two-subtest forms, Vocabulary and Matrix Reasoning. The vocabulary subscale is considered a reliable index of premorbid intelligence. The analytical description of the test and the corresponding Greek norms are available in (Wechsler 1999; Messinis and Papathanasopoulos 2009).

2.2.3 Verbal Learning and Memory

For the evaluation of verbal learning and memory, the Rey Auditory Verbal Learning Test (RAVLT) was used. The RAVLT evaluates the person's ability to encode, consolidate, store, and retrieve verbal information. The administration of RAVLT is a relatively easy task and thus it is preferred when clinicians are solely interested in examining participants' ability to learn lists of words, and not their fundamental organizational skills. In the present study, the administration was conducted in the following form: A 15-word list (list A) was orally presented and repeated five times (learning trials). After each trial, participants were asked to recall as many words as they could. After the fifth trial, a new list of 15 different words (List B or Distracter List) was presented only once. First, participants' ability to recall the second list was evaluated, and then participants were instructed to recall as many words as they could from the first list. After 25 min, a free recall trial was performed, and then a memory recognition trial using a word list containing target words, namely, previously presented items, and new words that acted as distracters. The dependent variables in this study were the average number of total words recalled: in each of the five learning trials, in the total learning of trials 1–5 and in the delay recall trial. For the analytical description of the RAVLT and the corresponding Greek norms, visit (Messinis et al. 2007).

2.2.4 Verbal Fluency

For the assessment of verbal expression/fluency, the Greek verbal fluency task was used. The Greek verbal fluency task assesses the effectiveness of thought and has been found to be sensitive to dysfunction of the left frontal cortex. In this test, participants are asked to orally produce as many different words as possible within 60 s belonging to three predetermined categories (semantic fluency) or beginning with three designated letters (phonological fluency). The grading of the strategies used to perform the task provides useful information on how thinking is organized. The analytical description of the verbal fluency task and the corresponding Greek norms are available in (Kosmidis et al. 2004).

2.2.5 Mental Information Processing Speed and Working Memory

The Symbol Digit Modalities Test (SDMT) is a task in which participants, by using a reference key, have 90 s to pair specific numbers with given geometric figures. It is used to measure mental processing speed, working memory, and attention. The detailed description of the original SDMT is available in (Smith 2002) clinical manual, whereas the corresponding Greek norms can be found in (Argirokastritou et al. 2005).

2.2.6 Attention, Visual-Motor Speed and Set-Shifting Ability

The Trail Making Test (TMT), consists of Part A and Part B, and was used to assess attention, visual-motor speed, mental information processing speed, and set-shifting ability. In Part A, examinees are instructed to connect, by drawing lines on a sheet of paper, a set of 25 circled numbers in a numerical sequence as fast as possible. In Part B, participants must connect circled numbers (from 1 to 13) and letters (from A to M) in an alternating numeric and alphabetic sequence, as quickly as possible (e.g., 1-A, 2-B, etc.). Thus, Part A examines participants' visual-motor speed and attention, while Part B examines their mental information processing speed and their set-shifting ability. The dependent variable in this study was time completion only of Part B. The detailed description of both parts of TMT is available in (Armitage 1946). The corresponding Greek norms can be found in (Vlahou and Kosmidis 2002).

2.2.7 Assessment of Mood

To evaluate the severity of depressive symptoms, the Beck Depression Inventory—Fast Screen (Beck et al. 2000) was administered. This short version of the depression scale is suitable for assessing the presence and severity of depression in patients since it isolates the cognitive, from the physical symptoms of depression. The latter may overlap with organic symptoms due to neurological diseases (e.g., insomnia) (Beck et al. 2000).

2.2.8 Quality of Life

The WHOQOL-BREF self-report questionnaire was used to evaluate quality of life. The Quality of Life (QOL) questionnaire consists of 26 questions and it was created by the World Health Organization (WHOQOL Group 2004). Each question is rated on a 5-point Likert scale, in which 1 represents the absolute negative dimension (never, at all, extremely dissatisfied) and 5 the absolute positive dimension (too, very, extremely satisfied). The WHOQOL-BREF can be completed within 5–10 min and has very good reliability (ICC values for all thematic units: 0.80–0.87) and validity. The questions are divided into four domains: (a) physical health, (b) psychological health, (c) social relationships, and (d) environmental health. There are also two questions regarding the general quality of life in relation to health. Higher values in these domains imply better quality of life and vice versa. The average values of the healthy Greek sample were: (a) physical health 74.58 (SD = 13.40), (b) psychological health 66.79 (SD = 12.95), (c) social relationships 71.49 (SD = 13.70), (d) environmental health 54.06 (SD = 11.69), and for (e) general health 73.69 (SD =16.15) (see Ginieri-Coccossis et al. 2012).

2.3 Statistical Analyses

All data were collected and processed, using SPSS (version 23). The Kolmogorov–Smirnov test was used to evaluate the normality of data distribution. For normally distributed data, we used the parametric *t*-test, whereas for non-normally distributed data, we used the non-parametric Mann–Whitney *U*-test in order to compare group differences. The estimation of the effect size of the established group differences was calculated with Cohen's *d*. Gender ratio was tested using the chi square criterion. Moreover, to test which variables significantly contributed to neuropsychological function and to examine their correlation to quality of life as well as clinical and demographic variables, logistic regression analyses were performed.

3 Results

3.1 Comparison of Demographic Variables Between Diabetic Patients and Healthy Controls

As for the variable of age, a parametric independent samples *t*-test revealed no statistically significant difference between the two groups [t (70) = 1.915, p = 0.06]. Similarly, a non-parametric Mann–Whitney test demonstrated no significant difference between the two groups, for education, ($z = -1.037$, $p = 0.300$). For the gender ratio, the chi square test showed a statistically significant difference between the male and female frequency only in the diabetic group, favoring male participants [χ^2 (1) = 4.157, p = 0.041].

Furthermore, the performance of the two groups on the MMSE and the WASI tests was compared. The results revealed no statistically significant difference between the two groups in any of the two tests (MMSE: $z = -1.472$, p = 0.125, WASI: $z = -8.59$, $p = 0.348$). Thus, overall results showed that the two groups were well balanced in terms of demographic characteristics and cognitive reserve; variables which could affect participants' performance in the experimental cognitive tasks. The two groups, however, varied in terms of depression levels, with the clinical group showing a higher level of depression, as was expected, [t (70) = 0.190, p = 0.011] (see also Table 1).

3.2 Comparison of Cognitive Variables Between Diabetic Patients and Healthy Controls

Table 3 presents the performance of the two groups on the cognitive tasks and the results obtained from the comparison between their performances in each task. Results revealed statistically significant differences between the two groups in all

Table 3 Comparison of neuropsychological performance between type 2 diabetic patients and healthy controls. Mean: (SD)

Task	Group	Mean (SD)	Mann-Whitney test (z-score)	p-value	Cohen's d effect size
RAVLT1	T2DM	4.02 (1.56)	−5.118	0.000∗	1.56
	CG	6.71(1.86)			
RAVLT2	T2DM	6.39 (1.87)	−4.372	0.000∗	1.20
	CG	8.46(1.55)			
RAVLT3	T2DM	6.73 (2.17)	−5.031	0.000∗	1.40
	CG	9.61 (1.93)			
RAVLT4	T2DM	6.45 (2.05)	−5.754	0.000∗	1.99
	CG	10.07(2.17)			
RAVLT5	T2DM	6.64 (2.06)	−8.307	0.000∗	2.02
	CG	10.64(1.89)			
RAVLT TOTAL	T2DM	29.77 (7.65)	−8.318	0.000∗	2.03
	CG	45.66(8.03)			
RAVLT DELAY RECALL	T2DM	5.32 (2.48)	−2.846	0.004∗	1.46
	CG	8.86 (2.34)			
SEMANTIC FLUENCY	T2DM	32.00 (7.92)	−3.799	0.002∗	0.86
	CG	41.50(13.32)			
PHONEMIC FLUENCY	T2DM	21.75 (7.78)	−3.458	0.001∗	0.87
	CG	30.50(11.78)			
SDMT	T2DM	30.48(14.26)	−2.497	0.001∗	0.62
	CG	38.21 ± 10.10			
TMTB	T2DM	179.36 ± 91.01	−2.859	0.004∗	0.93
	CG	111.86 ± 45.74			

T2DM Type 2 Diabetes Mellitus, *CG* Healthy control group
∗ Significant at< 0.005

cognitive domains assessed, with the control group performing better that the diabetic patients (see Fig. 1). The estimation of the effect size (degree of variability), as revealed from the comparison between the two groups' performance on the cognitive tasks, showed that there was a medium-sized group effect (Cohen's d = 0.5–0.8) on the SDMT task, whereas large-scale group effects were demonstrated in the rest of the variables (Cohen's $d \geq 0.8$), especially those that assess verbal learning and episodic memory.

3.3 Contribution of Demographic and Clinical Variables on Diabetic Patient's Neuropsychological Performance

In order to investigate the contribution of demographic and clinical variables on the neuropsychological performance of diabetic patients, we conducted a series of multiple regression analyses, with the cognitive variables inserted as dependent

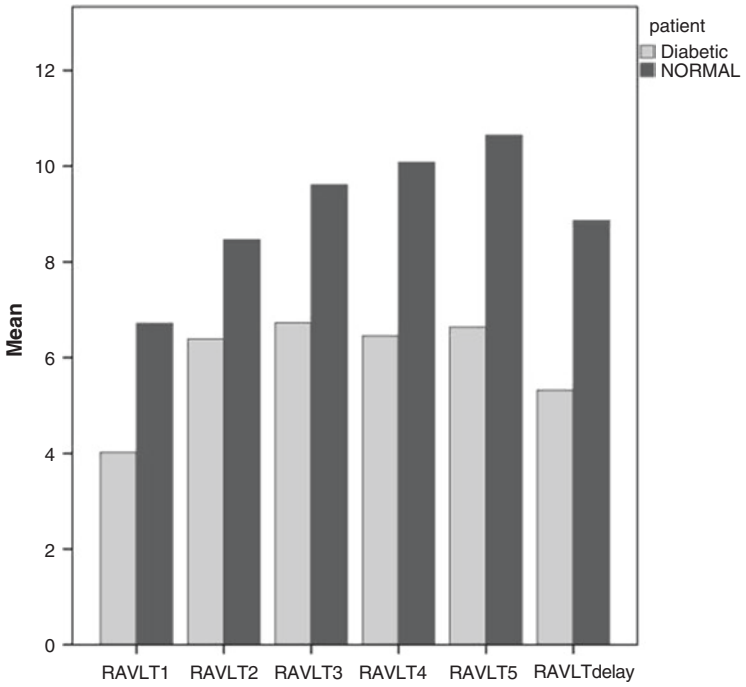

Fig. 1 Mean performance of type 2 diabetic patients and healthy controls on the verbal learning and delay recall trials of the RAVLT

variables and the demographic (age, years of education, gender, premorbid intelligence level), and clinical variables (depression level, body mass index (BMI), insulin levels, glycosylated hemoglobin levels, smoking) inserted as independent variables. Our results revealed that glycosylated hemoglobin levels accounted for 28% of the variance (R2 = 0.28; F = 16.584, $p < 0.001$) on the total verbal learning ability (RAVLT total learning trials 1–5) of diabetic patients. Furthermore, glycosylated hemoglobin levels accounted for 34% of the variance (R2 = 0.34; F = 13.541, $p < 0.047$) on verbal episodic memory delay recall ability (RAVLT delay recall trial) of diabetics. From the demographic variables, the interaction of age, education, and premorbid intelligence level accounted for 23% of the variance (R2 = 0.23; F = 10.512, $p < 0.001$) on the RAVLT learning trial 5, 26% (R2 = 0.26, F = 12.933, $p = 0.008$) on the RAVLT total learning trials 1–5 and 21% of the variance (R2 = 0.31; F = 18.145, $p = 0.043$) on the RAVLT delay recall trial. Moreover, the interaction of age and estimated premorbid intelligence accounted for 21% of the variance (R2 = 0.21; F = 10.268, $p = 0.001$) on the TMT-B cognitive task (executive function and set-shifting ability) and 37% of the variance (R2 = 0.37; F = 11.179, $p = 0.016$) on the SDMT (attention, mental information processing speed, working memory). The remaining variables were not found to significantly contribute to the neuropsychological performance of diabetic patients.

3.4 Contribution of Neuropsychological Performance on the Quality of Life in Diabetic Patients

In order to investigate the contribution of neuropsychological performance on perceived quality of life as measured by the WHOQOL-BREF questionnaire (physical health, psychological, social health, environmental health, and general health) in our type 2 diabetic patients, we divided these patients, into two subgroups, based on their different levels of cognitive performance. The first group (NIC) consisted of patients whose cognitive performance was not considered impaired (i.e., performed up to 0.5 SD below the normative data for each measure), whereas the second group (IC) consisted of patients whose performance was considered impaired (i.e., performed at least ≤1.5 SD below the normative data for each utilized measure). By forming subgroups of diabetic patients, based on their different levels of cognitive performance, we found that 16 out of 42 patients (38.10%) had performance of up to 0.5 SD lower than the normative data on the RAVLT total learning trials 1–5, whereas 26 out of 42 patients (61.90%) had a performance of at least ≤1.5 SD lower than the normative data on the RAVLT total learning trials 1–5. Moreover, statistically significant differences were attested on the WHOQOL-BREF questionnaire in the domains of "psychological health" [t (40) = 2.502, p = 0.017] and "environmental health" [t (40) = 2.643, p = 0.012], based on RAVLT total verbal learning trial 1–5 performance, with the cognitively impaired diabetic group showing poorer QOL on both domains compared to the cognitively unimpaired diabetic group. No other statistically significant differences were noted (see Table 4).

Based on the different levels of cognitive performance on Part B of the TMT test, 11 out of 42 patients (26.20%) had unimpaired cognition, while 31 out of 42 patients, namely, 73.80%, had impaired cognition. Comparisons between the two subgroups' performance on the WHOQOL-BREF and the TMT-Part B,

Table 4 Comparison of quality of life (QOL) and performance on the RAVLT total learning trials 1–5 between the two diabetic subgroups

WHOQOL-BREF	RAVL total	*N*	Mean	SD	Std. error mean
Physical health	NIC	16	63.06	11.369	2.842
	IC	26	56.62	13.983	2.742
Psychological health	NIC	16	65.69	9.666	2.416
	IC	26	55.04	15.199	2.981
Social relationships	NIC	16	70.25	16.675	4.169
	IC	26	59.46	18.470	3.622
Environmental health	NIC	16	68.50	9.839	2.460
	IC	26	56.62	16.199	3.177
General health	NIC	16	62.31	16.459	4.115
	IC	26	57.96	18.773	3.682

NIC Non-cognitively impaired diabetic group, *IC* Cognitively impaired diabetic group, *RAVLT* Rey Auditory Verbal Learning Test

demonstrated statistically significant differences between the two groups on the "social relationship" [t (40) = 2.557, p = 0.014], and "general health" domains [t (40) 2.773, p = 0.009], with the cognitively impaired diabetic patients performing poorer in both QOL domains. No other statistically significant differences were found (see Table 5).

Considering the different levels of cognitive performance on the semantic fluency task, 28 out of 42 patients (66.67%) had unimpaired cognition, while 14 out of 42 patients, namely, 33.33%, had impaired cognition. Comparisons between the two subgroups' performance, on WHOQOL-BREF and the semantic fluency task, demonstrated a statistically significant difference between the two groups, only on the domain "environmental health" [t (40) = 2.191, p = 0.034], with the cognitively impaired diabetic patients performing poorer on this QOL domain. No other statistically significant differences were noted (see Table 6).

Table 5 Comparison of quality of life (QOL) and performance on the TMT-Part B between the two diabetic subgroups

WHOQOL-BREF	TMT B	*N*	Mean	SD	Std. error mean
	NIC	11	60.59	12.530	3.039
Physical health	IC	31	58.04	13.936	2.787
	NIC	11	63.18	9.671	2.346
Psychological health	IC	31	56.32	16.237	3.247
Social relationships	NIC	11	65.82	20.100	4.875
	IC	31	62.04	17.372	3.474
Environmental health	NIC	11	61.06	15.143	3.673
	IC	31	61.20	15.468	3.094
General health	NIC	11	62.18	21.270	5.159
	IC	31	57.88	15.325	3.065

NIC Non-cognitively impaired diabetic group, *IC* Cognitively impaired diabetic group, *TMT Part B* Part B of the Trail Making Test

Table 6 Comparison of quality of life (QOL) and performance on the semantic fluency task between the two diabetic subgroups

WHOQOL-BREF	Semantic fluency	*N*	Mean	SD	Std. error mean
	NIC	28	60.43	14.046	2.654
Physical health	IC	14	56.36	11.626	3.107
	NIC	28	60.79	13.585	2.567
Psychological health	IC	14	55.71	15.384	4.112
	NIC	28	66.57	14.911	2.818
Social relationships	IC	14	57.57	23.359	6.243
	NIC	28	64.61	13.417	2.536
Environmental health	IC	14	54.21	16.507	4.412
	NIC	28	60.07	19.335	3.654
General health	IC	14	58.71	15.066	4.027

NIC Non-cognitively impaired diabetic group, *IC* Cognitively impaired diabetic group, *TMT Part B* Part B of the Trail Making Test

3.5 Comparison of Cognitive Performance in Type 2 Diabetic Patients According to Their Employment Status

We further compared the neurocognitive performance of employed and nonemployed diabetic patients. Results revealed that employed diabetic patients performed significantly better only on Part B of the TMT, in that they completed the test much faster, and showed better cognitive flexibility skills, compared to nonemployed diabetic patients (see also Table 7).

Table 7 Comparison of cognitive performance in type 2 diabetic patients according to their employment status

Measure	Employed (8/42) Not employed (34/42)	Mean (SD)	Std. error mean	Mann–Whitney test (z-score)	*p*-value
RAVLT 1	Yes	4.63 (1.40)	0.498	1.144	0.259
	No	3.91 (1.62)	0.278		
RAVLT 2	Yes	6.75 (1.75)	0.620	0.527	0.601
	No	6.35 (1.95)	0.335		
RAVLT 3	Yes	7.75 (2.05)	0.726	1.333	0.190
	No	6.65 (2.11)	0.363		
RAVLT 4	Yes	6.88 (1.88)	0.666	0.530	0.599
	No	6.44 (2.12)	0.364		
RAVLT 5	Yes	6.75 (1.66)	0.590	−0.18	0.985
	No	6.76 (2.10)	0.361		
RAVLT TOTAL	Yes	31.00 (6.21)	2.196	0.350	0.728
	No	29.94 (8.03)	1.367		
RAVLT DELAY	Yes	6.50 (2.77)	0.982	1.506	0.140
RECALL	No	5.03 (2.41)	0.415		
SEMANTIC	Yes	34.13 (8.69)	3.073	0.915	0.365
FLUENCY	No	31.29 (7.68)	1.319		
PHONEMIC	Yes	23.25 (7.40)	2.617	0.717	0.477
FLUENCY	No	21.09 (7.72)	1.325		
SDMT	Yes	40.38 (18.51)	6.546	2.211	0.060
	No	28.29 (12.71)	2.180		
TMTB (sec)	Yes	119.00 (78.96)	27.919	−2.209	**0.031**[a]
	No	90.57 (15.53)	15.534		

[a]Statistically significant $p < 0.05$

4 Discussion

Type 2 diabetes is emerging as a major global health issue, associated with reduced health-related quality of life (HRQOL) and also adversely affecting cognitive function. The objectives of the present study was to investigate the cognitive performance of type 2 diabetes mellitus patients as well as to examine disease variables that may contribute to cognitive dysfunction in this population and the associated HRQOL of type 2 diabetics with neuropsychological deficits.

Results showed that diabetic patients and healthy participants were well matched on baseline comparisons, regarding demographic variables (age and level of education) that could influence the performance of the cognitive measures. Our groups were also well balanced in relation to the estimated premorbid intelligence, which is an important predictor of cognitive function in this population (Wong et al. 2014). In support of this issue, a study with the Lothian Birth Cohort found that intelligence level at age 11 was an important predictor of cognitive ability in middle and older ages (Gow et al. 2011). Moreover, a more recent study reported that young adult military recruits with the lowest scores on general intelligence tests had twice the risk of diabetes incidence than those with the highest scores (Twig et al. 2014). Our patients and healthy controls were also well matched in terms of general mental state. On the other hand, there were significantly more male diabetic participants, a finding that is not surprising if one considers the male–female ratio of these patients in the general population (Wild et al. 2004). In terms of mood status, diabetic patients had higher levels of depression, as was expected (Zurita-Cruz et al. 2018), due to the chronic nature of the disease. It must be noted, however, that the depression scale reached only minimal to mild levels, which are considered to have a relatively small impact on neurocognitive function.

In terms of cognitive functioning, the diabetic group performed quantitatively worse compared to healthy participants on all the cognitive domains that were objectively assessed. More specifically, significant differences were noted on the measures of verbal learning and episodic memory, mental information-processing speed, attention, verbal fluency, and executive functions. The episodic memory subdomains of "immediate memory," "total learning rate," and "delay recall" all had large-sized group effects, confirming earlier studies that had found increased prevalence rates and large effect sizes of these deficits in type 2 diabetics (Lee et al. 2014; McCrimmon et al. 2012; Whitmer 2007; Koekhoek et al. 2015). On the other hand, the executive function of the set-shifting ability was only marginally above the level of medium-sized group effect (0.93), whereas mental information-processing speed, attention, and working memory had a medium-sized group effect, confirming two recent meta-analytical studies (Palta et al. 2014; Sadanand et al. 2016). Moreover, our results showed that the majority of the diabetic patients were considered cognitively impaired on the objective measures of verbal learning and executive function, whereas for semantic fluency the majority of diabetics (66%) were found to be intact. A clinical translation of our findings may be related to the consequences these deficits have on everyday functioning and health-related quality of life. For

example, even mild to moderate deficits on episodic memory and executive functions may influence diabetes self-management behaviors, such as diabetes-specific numeracy ability, diabetes knowledge, insulin adjustment skills and learning to perform insulin injections, missed appointments, worse adherence to medications, and reduced self-care activities and self-care outcomes (Tomlin and Sinclair 2016). Furthermore, diabetic patients' perceptions of their cognitive difficulties may assist clinicians and other health care providers in detecting deficiencies in terms of performing diabetes self-management tasks (Cuevas and Stuifbergen 2017).

Our investigation of demographic and clinical risk factors that could potentially contribute to cognitive impairment revealed that an interaction of age, level of education, and premorbid intelligence explains a relative proportion of the variance on verbal learning and episodic memory performance. In addition, the interaction of age and premorbid intelligence contributes to cognitive performance, and on a smaller scale on set-shifting ability and verbal fluency performance. On the contrary, it appears that the interaction of age and premorbid intelligence has the highest contribution in terms of demographic variables on the domains of mental information processing speed and working memory. These results are consistent with various studies that have noted that older patients, with a lower cognitive reserve (i.e., premorbid intelligence and educational level), have poorer cognitive ability (McCrimmon et al. 2012). It is common knowledge that as type 2 diabetics age, they develop various comorbidities such as atherosclerosis, hypertension, and macro-microvascular disease that lead to further cognitive decline (Lee et al. 2014; McCrimmon et al. 2012).

In terms of clinical variables, we found that only glycosylated hemoglobin levels contributed to verbal learning and episodic memory capacity. This finding confirms a recent meta-analysis (Mansur et al. 2018) that identified an association between decreased glycemic control and cognitive impairment. A clinical extension of this result may implicate that, by improving glycemic control, patients may reduce the potential of developing verbal episodic memory deficits.

Although 1/5 of our diabetic patients were smokers, we found no significant effects on the cognitive performance outcome of current smokers. However, as the duration and frequency of smoking may influence the actual impact of this factor on cognition, our findings could potentially have been different if our sample of diabetics were heavier and more chronic smokers. We did not, however, explore the duration and frequency of smoking on cognition in this study.

Our finding is considered inconsistent with the literature, which generally supports a negative association between tobacco smoking and cognitive function, even from young adulthood (Chamberlain et al. 2012). Moreover, smoking is considered a major risk factor for developing diabetes, with 12% of type 2 diabetic cases being attributed to tobacco smoke (45% higher in men, 74% higher in women, compared to nonsmokers) (Prasad and Cucillo 2015). Major pathological changes in diabetic patients such as insulin resistance and high levels of glycated hemoglobin (HbA1c) are also considered common in smokers (Prasad and Cucillo 2015). Moreover, depressive symptoms were not significantly related to any of the cognitive domains we assessed. This is probably due to the fact that mean levels

of depression in our diabetic sample were considered mild. Moderate to higher levels of depression are potentially required in order to have a negative impact on cognition. This is clearly evident from an interesting study with a large sample of type 2 diabetics, which reported accelerated cognitive decline amongst patients with at least moderate levels of depression on the 9-item Patient Health Questionnaire (Sullivan et al. 2013).

As mentioned previously, T2DM patients have poorer quality of life compared to healthy persons, which is associated to a multitude of health-related factors, including duration of diabetes, impaired glucose tolerance, comorbidities, loss of employment, presence of depression, and older age (Vaatainen et al. 2014; Zurita-Cruz et al. 2018; Trikkalinou et al. 2017; Lu et al. 2017). In this study, we found that the mean performance of diabetics with cognitive impairment on verbal learning, episodic memory, and executive dysfunction, was lower than the mean performance of the healthy controls (see Ginieri-Coccossis et al. 2012) in the four basic QOL dimensions (physical health, psychological and social relationships, as well as environmental health). Furthermore, our study revealed that diabetic patients with impairment on various cognitive domains had poorer quality of life in specific dimensions. More specifically, patients with impaired verbal learning capacity had lower performance on the QOL dimensions of psychological and environmental health. In addition, patients with deficits on executive functioning had poorer performance on the QOL dimensions of social relationships and general health. Patients with verbal fluency deficits had poorer environmental health. The implications of these findings for everyday functioning and overall quality of life are important. Patients with episodic memory difficulties may have difficulty acquiring new information and skills, and possibly have a higher forgetting rate, associated with negative feelings, lower self-esteem, and reduced opportunities for leisure activities. Similarly, diabetics with executive dysfunction may become less cognitively flexible and have difficulties planning, organizing, and completing everyday mentally demanding, effortful tasks or with interpersonal and social relationships, and overall activities of daily living. Interestingly, (Theofilou 2009) reported that the perception of the QOL dimension of environmental health is influenced by the educational level of the patients. Moreover, several studies conducted on elderly healthy participants, who are often considered to have similar characteristics and associated cognitive impairment with T2DM patients, showed that they have low levels on the QOL dimension of psychological health (Apostolou and Gokal 2000; Chiang et al. 2004; Vasilieva 2006). What remains unanswered, however, in the international literature is the impact that neuropsychological impairment may have on the HRQOL of type 2 diabetics. With this in mind, a recent cross-sectional study was conducted (Aithal et al. 2018) in 52 type 2 diabetic patients (mean age 65.79 years), with the majority treated via oral hypoglycemic medications and about 26 of the subjects reported the disease duration to be less than 5 years. They were additionally diagnosed with mild cognitive impairment and given the WHOQOL-BREF questionnaire, which as described

previously, is based on four domains: (i) physical health, (ii) psychological and (iii) social relationships, and (iv) environmental domain.

The study revealed that QOL was decreased in this cognitively impaired diabetic population with the most affected domains being the psychological (mean = 50.73) and the social relationships (mean = 46.48). Furthermore, negative correlations were established between QOL domains and MMSE scores. The findings of our study are in accordance with the results reported by (Aithal et al. 2018), especially regarding the most affected QOL domains (psychological and environmental health) in our patients with episodic memory difficulties. It is worth noting that deficits in episodic memory are also common in patients with amnestic mild cognitive impairment, as were most of the diabetic patients assessed in the referred study (Aithal et al. 2018). Patients in our study were, however, on average much younger than the patients of the (Aithal et al. 2018) study and their MMSE scores were in the normal range. In this respect, we may assume from our findings that middle-aged diabetic patients with a normal general mental state, but with specific neuropsychological deficits have lower perceived QOL in the respectively affected domains.

Another important indicator of everyday functioning ability that largely contributes to overall QOL is employment status. In the present study, we compared the neuropsychological functions of employed and nonemployed T2DM patients. Our results revealed that employed diabetic patients had better executive function skills, especially cognitive flexibility and mental processing speed. As previously noted, these types of higher-order executive functions significantly contribute to a person's planning and organizing capacity and their ability to complete everyday mentally demanding tasks, as is usually required in employment settings. Our findings confirm recent results from a Canadian study (Lee et al. 2017) that found cognitive symptoms to be positively correlated to workplace impairment among participants with or at risk to develop type 2 diabetes. The authors conclude that impaired glucose regulation is mediated principally by their self-rated cognitive dysfunction.

Although our study has several strengths, including the reduced effect of potential confounders on cognitive performance, that is, the well-matched baseline demographic characteristics and premorbid intelligence of the two groups; the comprehensive assessment of cognition utilizing multiple standardized measures, sensitive in type 2 diabetics; the validated with Greek participants quality of life measure, there are some potential limitations. These include the size of the diabetic groups, after being divided into two subgroups (based on their different levels of cognitive performance) in order to assess the influence of cognitive impairment severity on QOL; the potentially unknown and subclinical complications, which may have not been accounted for and might have a bearing on neuropsychological performance; the exclusion of type 2 diabetics with poorer global cognitive ability. Including patients with a poorer global cognitive state may have differentially influenced the outcome of QOL results. However, excluding globally cognitive impaired patients may also be considered a strength of the study as noted previously in the text.

5 Conclusions

Cognitive impairment is considered an increasingly important complication of type 2 diabetes. Here we report a novel finding regarding the association between middle-aged diabetic individuals with a normal general mental state, but with neuropsychological deficits on verbal learning, episodic memory, executive function, and domain-specific decreased QOL. Although our findings conform to the notion that cognitive deficits occur subsequent to diabetes, and functional MRI studies have demonstrated reduced activation in T2DM patients in regions relevant to neuropsychological task performance, other explanations are possible. For example, childhood variables may strongly affect adult cognitive function, and adverse socioeconomic circumstances early in life can increase the risk of both T2DM development and later-life cognitive dysfunction. Moreover, diabetes-related cognitive dysfunction may be primarily or partly of vascular origin, requiring prolonged disease periods or interaction effects between normal aging and diabetes.

More important, however, for clinical purposes, is how clinicians should frame discussion of cognitive difficulties with their diabetic patients. At present, routine clinical practice includes information provision about diabetes and its related complications to patients, when they are learning how to manage their diabetes and the associated risk factors. Informing the diabetic individual that cognitive impairment is an inevitable complication of diabetes is likely to cause great concern and anxiety to the patient, resulting in negative psychosocial effects. From this perspective, it is extremely important that research efforts continue to clarify the clinical significance and implications of cognition on everyday functioning abilities and quality of life of diabetics. Moreover, improved methods of identifying and detecting modifiable risk factors might delay or prevent clinically relevant cognitive impairment. Lastly, health care providers should be presented with the opportunity to improve or motivate optimum diabetes self-management tasks.

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Ethics Approval and Consent to Participate The study was approved by the Ethics Committee of the University Hospital of Patras.

Human and Animal Rights No animals were used in this study. For our human subjects, the study protocol and research was approved by the Ethics Committee of the University Hospital of Patras, according to the Helsinki Declaration of 1975, as revised in 2008.

Consent for Publication Written consent was obtained from all participants of the present study after having been informed of the nature of the study they would take part in.

Conflict of Interest The authors declare no conflict of interest, financial or otherwise.

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A Framework for Assessing the Impact of Information-Seeking Behavior on Cancer Patients' Long-Term Prognosis

Evangelos Persakis and Petros Kostagiolas

1 Introduction

Cancer is considered as a globally occurring, life-threatening disease (WHO 2018). Despite the slight decrease of overall cancer fatality rates in most developed countries, the application of proven preventive measures should be a priority of healthcare systems (Siegel et al. 2017). Chronic uncertainty and anxiety of cancer patients' regarding their health status can be a significant psychological burden (Armes et al. 2009). Indeed, providing proper information so as to satisfy the oncological patients' information needs is proven to be beneficial, improve patients' health-related quality of life and decrease symptoms of anxiety and depression (Faller et al. 2016). This area of knowledge is rich and involves extensive exploitation of the impact of information on patients' decisions regarding their treatment and their overall long-term prognosis (Fiszer et al. 2014; Husson et al. 2011). Below, a framework for assessing the impact of information-seeking behavior on cancer patients' long-term prognosis is provided. This conceptual framework is theoretically grounded, while well-documented constructs are pooled from the literature and framed together in order to provide means for measuring the embedded concepts.

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2 Conceptual Frameworks

It has long been established that proper information technologies, practices, and behaviors affect the long-term prognosis of cancer patients and benefit cancer management (Oerlemans et al. 2012). For instance, previous studies suggest information conceptual frameworks for cancer patients (Arora et al. 2007a) based on behavioral models (Andersen 1995) and patient outcomes (Wilson and Cleary 1995). The abovementioned frameworks and models are grounded in theories explaining how information is embedded within our life situations, predicaments, and roles, that is, the "uncertainty reduction theory" (Wilson 1999b) and the "stress coping theory" (Savolainen 2011; Strack and Deutsch 2011; Hofmann et al. 2008). The first explains how "information" can be used: (i) to manipulate the uncertainty of cancer care management, following medical procedures and medication, and (ii) for constant cooperation with the healthcare professionals. Uncertainty has been defined as a lack of information about an event, and it also has been characterized as an aversive state that people are motivated to reduce (Savolainen 2011; Wilson 1999b; Wilson et al. 2002). The availability of reliable and proper information decreases uncertainty (Brashers 2001) and thus empowers patients in their role regarding cancer management. It also increases their understanding of their clinical situation and the available treatment options for all cancer stages. Thus, according to this theory, information is strategically important for decreasing uncertainty when dealing with cancer. In that respect, patients' engagement in information-seeking is a goal-directed behavior with the resolution of the "problem" as a goal (Wilson 1999a).

According to the second theory, "coping" refers to the interaction between a person and their environment under stressful circumstances, such as cancer. Human behavior is not a unified phenomenon but it is determined by different psychological mechanisms (Strack and Deutsch 2011). Cancer patients' behavior has been further described in the literature by mechanisms explaining the interaction of impulsive influences with components of reflective determination (Strack and Deutsch 2004). Patients' health information-seeking behavior could be predicted by the combination of impulsive precursors (automatic approach—avoidance reactions; automatic affective reactions), of reflective precursors (restraint standards; reasoned attitudes), and of boundary conditions (cognitive load; ego depletion; habitualness; mood) (Hofmann et al. 2008). Individual characteristics such as beliefs as well as the availability of resources including time and information are important for successful stress-coping (Smelser and Baltes 2001). Proper information can help the patients appraise a situation or an event as negative, as neutral or as positive in the sense of a challenge to be tackled. These, among other, prevalent theoretical justifications underline not only the medical conditions an individual may face, but also point out the important role of information in several domains, including cognitive, affective, and social behaviors, abilities, adaptation skills, motivation mechanisms, social and work roles.

To systematically review the role of information in health outcomes of cancer patients a three-stage conceptual framework that identifies the association of

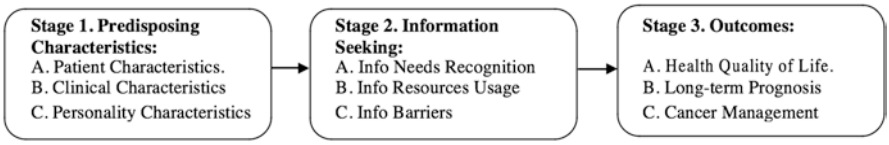

Fig. 1 A Framework for the impact of information-seeking behavior on cancer patients' long-term prognosis

patients' long-term prognosis with several sociodemographic, clinical, psychological, and information behavioral factors is developed and presented (Fig. 1). In this approach, the first stage includes important "predisposing characteristics" such as: (a) patients' sociodemographic characteristics (such as sex, age, education level, marital status, employment status); (b) patients' clinical characteristics (such as cancer type, grade, treatment, recurrence, comorbidity, late effects, anxiety); and (c) patients' personality characteristics (such as perceived health competence, fear of progression, health locus of control).

2.1 Information-Seeking Behavior

The second stage involves the patient's health information-seeking behavior, which directly relates to the first stage through Wilson's macro-model for information-seeking analysis (Wilson 1999a). Wilson's approach to information-seeking is based on recognition of human "needs" (in our case, the recognition of the patients' "needs"), which might be psychological, affective, and cognitive. These "needs" are immerging with the aim to be satisfied so an individual might cope better with their situation and reduce the uncertainty inherited in making and/or participating in cancer management decisions, during a long cancer treatment/management path.

The patients typically seek information in a combination of the wide range, conventional, digital, and/or interpersonal information resources that are available. Finally, when seeking information, individuals face a number of barriers that may be personal, interpersonal, and environmental (Wilson 2006). Cancer-related information literacy competences and skills are important in order to choose and thereafter utilize in an efficient and effective way the available health information resources (Sparks and Nussbaum 2008). Finally, the third stage of the macro-model presented in Fig. 1 refers to health outcomes such as: (a) health-related quality of life, (b) long-term clinical prognosis, and (c) cancer management.

The next three subsections present the analysis for each of the model stages; while supporting literature for relating predisposing patient characteristics to long-term prognosis of cancer patients, through patients' information-seeking behavior is summarized in Table 1.

Table 1 Supporting literature for relating information seeking to long-term prognosis of cancer patients

Framework stages	Cancer patient information seeking related suggestions	Indicative references
1. Predisposing characteristics		
1a. Patients characteristics	Cancer patients' young age is considered as a predictor of higher levels of information needs. Positive association among education, living with a partner, and cancer patients' information satisfaction.	Fiszer et al. (2014) Henry et al. (2014)
1b. Clinical characteristics	Negative association between disease remission and patient's information needs. Negative association between comorbidity and patient's information satisfaction. Greater satisfaction of unmet patient information needs is related to less anxiety.	Faller et al. (2016) Oerlemans et al. (2012) Husson et al. (2011)
1cl. Perceived health competence	Positive patient perceptions of health competence are associated with helpful informational support. Higher levels of patient perceived health competence could ensure greater patients' satisfaction with the received information.	Arora et al. (2007b) Husson et al. (2013)
1c2. Fear of progression	Oncological patients would experience less persistent fear of recurrence and stress through improved information provision. The comprehensibility of the information provided could reduce patients' fear of cancer progression. Higher levels of fear of progression are associated with inadequate health literacy.	Crist and Grunfeld (2013) Gross et al. (2015) Halbach et al. (2016)
1c3. Health locus of control	Greater patients' perception of control of their health is related to their information satisfaction.	DeRouen et al. (2015)
2. Information seeking behavior		
2a. Info needs	Information about treatment is one of the most important cancer information topics.	Shea-Budgell et al. (2014)
2b. Info resources	Healthcare professionals are one of the main sources of health information for oncological patients.	Rutten et al. (2016)
2c. Info barriers	Low levels of information-needs satisfaction is a barrier to cancer patients' information seeking.	Li et al. (2011)
2d. Info needs satisfaction	A higher patients' information needs satisfaction is predicted by better health-related quality of life.	Rood et al. (2015)
3. Health outcomes		
3a. Health – related quality of life	Less satisfied with information received cancer patients have lower quality of life.	Faller et al. (2016)
3b. Long – term prognosis	More barriers to patients' information seeking are associated with worse mental and physical condition.	McInnes et al. (2008)

2.2 Predisposing Characteristics

The predisposing characteristics are unique for each individual and play an important role in oncological patients' information-seeking behavior and health outcomes. Patient and clinical characteristics, and factors concerning a patient's personality, are considered in our study as the main components of the predisposing characteristics. Patient characteristics include gender, age, education, marital status, and employment status (Ganz et al. 2002), whereas cancer type, grade, treatment, recurrence, comorbidity, and late effects are classified as clinical characteristics (Potosky et al. 1999). Patients' perceived health competence, their health locus of control and fear of disease progression could characterize their personality. More positive patient perceptions of health competence and greater participation self-efficacy have been associated with helpful informational support from healthcare providers (Arora et al. 2007b). Higher levels of fear of progression have been associated with inadequate health literacy in the elderly cancer patients (Halbach et al. 2016) and unmet patient health-informational needs (Sarkar et al. 2015). Furthermore, oncological patients' lower satisfaction with the type and timing of information provided, has been associated with lower levels of patients' health locus of control (Iskandarsyah et al. 2014).

2.3 Information-Seeking and Informational-Needs Satisfaction

Cancer patients' perception of risk of disease recurrence, level of competence in taking care of their health, and perception of control of their health might function as media for the improvement of their health outcomes under the impact of patient information-seeking behavior. Patients' perceived health competence includes both outcome expectancies and behavioral expectancies (Smith et al. 1995). Lower patient perception of health competence could be a barrier to information access (Arora et al. 2002), whereas higher levels of patient perceived health competence could ensure greater satisfaction with the received information (Husson et al. 2013).

Cancer patients often experience the symptom of fear of progression that affects their health-related quality of life, in particular the mental health dimensions (Mehnert et al. 2006). Through improved information provision, oncological patients would experience less persistent fear of recurrence and stress (Crist and Grunfeld 2013). Furthermore, the comprehensibility of the information provided could reduce patients' fear of cancer progression (Gross et al. 2015). Oncological patients with higher education and those living with a partner are more satisfied with the information received. In addition, patients in complete remission have expressed fewer unmet informational needs (Faller et al. 2016). Young age has been considered as a predictor of higher levels of health information needs (Fiszer et al. 2014). Comorbidity has been negatively associated with patients' informational satisfaction (Oerlemans et al. 2012). Patients' health status could be influenced by their

own behavior (internal health locus of control), fate, other people, as well as by their physicians (external health locus of control) (Wallston et al. 1994).

2.4 The Role of Information in Health Outcomes

Information provision to cancer patients might be predictive of their health outcomes. Patients' health-related quality of life is considered as a useful measure of their health outcomes and it includes physical, emotional, cognitive, role, and social functioning, and symptoms such as anxiety, depression, fatigue, pain, insomnia, dyspnea, and appetite loss (Arraras et al. 2004). The information received by cancer patients could be classified into four categories: disease, diagnosis, treatment, and care (Arraras et al. 2010).

Patients expressing a considerable amount of informational needs have been identified with high degree of informational satisfaction (Davies et al. 2008). Satisfied patients with the information received report better global health-related quality of life (Aranda et al. 2005). On the other hand, barriers to oncological patients' information-seeking behavior have been associated with decreased mental and physical functioning (McInnes et al. 2008). Furthermore, generalized anxiety disorder is one of the most common anxiety disorders seen in cancer patients. Symptoms like irritability, restlessness, and nervousness determine this type of disorder (Spitzer et al. 2006). Better patient emotional functioning has been associated with fewer informational and psychological needs (Snyder et al. 2008). Greater satisfaction of unmet patient informational needs has been related to less anxiety (Husson et al. 2011) and depression (Park and Hwang 2012).

3 Discussion

The loss of control over their everyday life reduces the overall health-related quality of life of adolescent and young adult patients with cancer (DeRouen et al. 2015). Fear of recurrence is a significant factor contributing to poor patients' quality of life (Kaur et al. 2014). Moreover, the higher the patients' satisfaction with the information provided, the better the health-related quality of life (Rood et al. 2015). Divorced cancer patients with unmet information needs experience a high level of anxiety and a diminished emotional quality of life (Henry et al. 2014). Furthermore, oncological patients with a great amount of unmet informational needs report greater anxiety and depressive symptoms and request further information provision concerning their disease (Faller et al. 2016). Psychological distress has also been associated with patients' psychosocial needs (Uchida et al. 2010).

As more types of cancer gradually become a disease that is considered to be a condition that patients can live with, as opposed to one they die as result of, healthcare professionals will be challenged to provide evidence-based guidance for the

long-term management of the patients' health. Oncologists should empower patients through information provision and guide them to good information-seeking practices. Physicians should persuade their patients to believe that they have the ability to deal with disease and reduce the level of distress by teaching coping strategies. Well-informed cancer patients are more likely to feel less anxious and to complete their therapy (Davies et al. 2008). Healthcare professionals should provide a positive feedback when patients have performed a successful information-seeking attempt, and not discourage them, because information should be considered as an essential component of cancer care (McInnes et al. 2008).

The conceptual model that associates cancer patients' clinical characteristics such as grade of cancer disease, comorbidities, treatments received, and late effects with the patients' emotional, physical, and cognitive status, could be completed by integrating requisite cancer-related information for hematological patients, such as non-Hodgkin's Lymphoma survivors (Arora et al. 2007a). Hodgkin's Lymphoma patients have to face problems that can affect their health-related quality of life (Oerlemans et al. 2011). Providing adequate information to cancer patients can improve the patients' health-related quality of life and their satisfaction with healthcare provision (Husson et al. 2011).

4 Conclusion and Further Research

To conclude, addressing unmet informational needs among cancer patients and finding ways to increase their sense of control seem crucial in improving their health-related quality of life and optimizing their health care. Lower informational satisfaction and more unmet needs are often associated with lower quality of life and higher anxiety and depression in cancer patients. Further studies should have a longitudinal design, from time of diagnosis until later stages of disease progression and treatment, in order to more precisely define the evolution of patients' informational needs during the course of illness. The conceptual framework utilized in this study, provides a useful model for future studies that are critical for enhancing our knowledge regarding the needs of this growing segment of the population. Additional research using more novel methods and measures can identify more influential aspects of the health information-seeking process.

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Sleeping Disorders and Health-Related Quality of Life in Hemodialysis Patients with Chronic Renal Disease in Greece

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1 Introduction

The NHANES III study, conducted in the United States (1988–1994) in a sample of 15.626 individuals, provided the first epidemiological evidence of chronic kidney disease (CKD), where 11% of the general population suffered from CKD (Ioannidis and Papadaki 2013). The European countries that have conducted such epidemiological studies are Norway and the United Kingdom. For Norway, 10% of the general population suffers from CKD, while in the United Kingdom, the rate for men and for women is 5.8% and 10.6%, respectively (Stevens et al. 2007; Hallan et al. 2006; Wasse and McClellan 2006). Other European countries have not yet reported any studies or outcomes of CKD at its various stages (Glassock and Winearls 2008; Schena 2000).

ERA-EDTA (European Dialysis and Transplant Association) is a European epidemiological study that collects and publishes statistical data from various European countries in relation to hemodialysis and renal transplantation. According to this study, 490,743 people required kidney support or kidney transplant in 2015. The ratio was 924 individuals per million inhabitants, the average age of these individuals was 60.9 years, and 62,962 suffered from diabetes mellitus (Kramer et al. 2018).

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The differences in the frequency with which CKD-FS (chronic kidney disease final stage) occurs and its prevalence in developed countries are due to racial/national differences, prevalence rates of diabetes mellitus, hypertension, as well as cardiovascular events in the respective countries (Madero et al. 2009; Shlipak et al. 2009; Hermans et al. 2007). The projected increase in the prevalence of CKD-FS is 5–8% per year. About 90% of people who are undergoing dialysis are mainly residents of developed countries. Nearly 1.7 million people are replacing their renal function, and only 1.3 million are under hemodialysis or peritoneal dialysis, while the others receive a transplant (National Kidney Foundation 2002). In Greece, about 10,000 people suffer from CKD-FS and undergo hemodialysis or peritoneal dialysis and/or kidney transplantation (Hellenic Society of Nephrology 2018).

Chronic renal failure, especially at the final stage, is a disease that highlights the importance of HRQOL to a very significant degree. Treating symptoms and continuing to long-term renal replacement therapy require constant dependence on healthcare services and radical changes of patients' lifestyles (Floege et al. 2010). Given the high prevalence of the disease and the high incidence of comorbidity, the need to identify the HRQOL factors, which are mainly involved in its degradation, is vital. By identifying these factors, appropriate adaptation of health systems, development of prevention and information, and more efficient design and distribution of the necessary resources can be achieved (Kramer et al. 2018; Ioannidis and Papadaki 2013).

The manifestations of the disease, the symptoms of the disease, and/or the treatment method, as well as the changes in the daily activities required, create a complex network of factors that interact with each other and generally decrease the quality of life (Avramovic and Stefanovic 2012; Theofilou and Panagiotaki 2010; Kutsopulu-Sofikiti et al. 2009).

Sleep disturbances are a frequent symptom in patients with CKD-FS, while researchers claim that the frequency is greater than what is recognized. The assessment of sleep quality in these patients is very important, as poor-quality sleep is associated, in addition to the decrease of HRQOL, with increased cardiovascular mortality (Hanly 2008). The presence of sleep disorders in people with end-stage renal disease significantly increases morbidity and mortality rates of the disease. The relationship between sleep disorders and kidney disease is complex and dynamic and has been poorly studied (Maung et al. 2016).

The aim of this study was to investigate sleep disorders and the level of health-related quality of life in hemodialysis patients with chronic renal failure.

2 Materials and Methods

This is a cross-sectional study. The study population consisted of patients with CKD-FS who underwent hemodialysis in Greece. The study took place from 5/11/2016 to 31/3/2017. In total, 700 questionnaires were distributed and 420 completed (60% response rate).

2.1 Tools

The Greek version of Kidney Disease and Quality of Life™ Short Form (KDQOL-SF™) v.1.2 was selected for the assessment of HRQOL of hemodialysis patients. It is a specialized tool for assessing HRQOL of hemodialysis patients. It includes 43 items related to the disease, 36 items from the SF-36 and a series of items about patient demographics and possible self-reported causes of renal disease (Hays et al. 1994).

The Pittsburgh Sleep Quality Index (PSQI) was used to investigate the quality of sleep of the participants. It is a specialized tool for assessing the quality of sleep and consists of 19 items. It estimates seven dimensions of sleep: subjective sleep, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The questionnaire has a diagnostic sensitivity of 89.6% and a specificity of 86.5% (kappa = 0.75, $p < 0.001$) in terms of the ability to distinguish between "good" and "poor" sleep quality (Buysse et al. 1989). The PSQI has been translated and validated in the Greek language (European Respiratory Society 2012).

2.2 Statistical Analysis

The statistical analysis was carried out using the IBM SPSS 21.0 statistical package. Descriptive statistics including frequencies and percentages were used to summarize participant demographic characteristics and responses. Pearson coefficient was used to explore the correlation between the dimensions of quality of life and sleep. The range of values varies between −1 and +1. Zero represents no correlation between two variables. Values 0.21–0.40 give small, 0.41–0.60 moderate, 0.61–0.80 strong, and >0.81 very strong correlation.

3 Results

The sociodemographics characteristics of the responders are presented in Table 1. Most of them were males (83.3%), aged 41–60 years (33.3%). About 74% were married, and 48% received less than 6 years of education. Thirty-one percent of responders had income of 3001–7000 euro/month, and eighty-one percent were retired.

The overall KDQOL results, by dimension of the quality of life considered, are given in Table 2. Each scaled is scored from 0 to 100, with 100 corresponding to a better quality.

Table 1 Sociodemographic data ($n = 420$)

Variables		*N*	%
Gender	Male	350	83.3
	Female	70	16.7
Age, years	21–40	40	9.5
	41–60	140	33.3
	61–75	140	33.3
	76+	100	23.8
Marital status	Unmarried	110	26.2
	Married	310	73.8
Education level	<6 years	200	47.6
	6–9 years	110	26.2
	9–12 years	40	9.5
	12–14 years	10	2.4
	University	60	14.3
Insurance	None	50	11.9
		370	88.1
Income, euro/month	<3000	50	11.9
	3001–7500	130	31.0
	7501–12,000	90	21.4
	12,001–20,000	80	19.0
	20,001–35,000	40	9.5
	>35,000€	10	2.4
	N/A	20	4.8
Type of employment	Full time	20	4.8
	Part time	30	7.1
	Unemployed	20	4.8
	Retired	340	81.0
	Disabled	10	2.4

Regarding the daily living limitation (ADL) (walking, crouching, raising stairs, etc.), the percentages of low HQOL are significant and range from 31% to 78.6% (Table 3).

Table 4 presents the analysis of factors based on the Pearson correlation coefficients, with coefficients of total patient health, physical function, physical role, pain, emotional well-being and emotional role, social function, energy/fatigue, effects and burden of nephropathy, and symptoms problems.

According to PSQI, 100 (23.9%) responders had good quality of sleep and 320 (76.1%) responders had poor quality of sleep. The average score of PSQI was 7.62 (with a cutoff limit of 5). Most of the responders did not receive any drugs to help them sleep (73.8%), while 7.1% received drugs less than 1 day/week and 19% more than 3 days/week.

Table 5 presents the analysis of factors based on the Pearson correlation coefficients, with coefficients of global PSQI score, subjective sleep quality, sleep latency,

Table 2 Results of KDQOL

Scale (N. items)	Mean ± SD
Symptoms (12)	69.7 ± 20.4
Effects of kidney disease (8)	44.9 ± 23.1
Burden of kidney disease (4)	40.1 ± 33.3
Work status (2)	25 ± 33.6
Cognitive function (3)	72.7 ± 21.7
Quality of social interaction (3)	69.4 ± 24.9
Sexual function (2)	39.6 ± 35.1
Sleep (4)	61.4 ± 20.3
Social support (2)	78.2 ± 21.9
Dialysis staff encouragement (2)	85.4 ± 21.7
Patient satisfaction (1)	82.9 ± 16.3
Total health (1)	50.7 ± 25
Physical function (10)	43.5 ± 33.5
Restrictions on role – due to physical problems (4)	36.9 ± 40.7
Pain (2)	57.1 ± 35.8
General health (5)	33.6 ± 20.6
Emotional wellness (5)	47.3 ± 25.9
Restrictions on role – due to emotional problems (3)	44.4 ± 40.8
Social function (2)	48.2 ± 33.4
Emotion/feeling of fatigue (4)	38.3 ± 27.2
SF-12 total physical health	**36.9 ± 11.9**
SF-12 total mental health	**39.6 ± 12.4**

Table 3 Percentages of severe limitations of daily physical activity

Activity	%
Jogging, heavy object picking, or difficult sports activities	78.6
Walking 1 km	59.5
Bathing or dressing	52.4
Scale escalation	51.2
Medium-intensity activities (table moving, vacuum cleaner, countryside walk, beach rackets)	45.2
Body bending, kneeling, crouching	45.2
Shopping (picking and/or transportation)	38.1
Walking a few hundred meters	35.7
Walking about 100 m	33.3
One-scale escalation	31.0

Table 4 Pearson analysis for patient's quality of life

Factors		Total health	PF	PR	Pain	EWB	ER	SF	E/F	Effects of nephropathy	Burden of nephropathy	Symptoms – problems
Total health	r	1										
	p											
Physical function	r	0.730	1									
	p	0.000										
Physical role	r	0.543	0.603	1								
	p	0.000	0.000									
Pain	r	0.595	0.518	0.694	1							
	p	0.000	0.000	0.000								
Emotional well-being	r	0.742	0.647	0.467	0.610	1						
	p	0.000	0.000	0.000	0.000							
Emotional role	r	0.614	0.430	0.433	0.405	0.661	1					
	p	0.000	0.000	0.000	0.000	0.000						
Social function	r	0.639	0.648	0.504	0.674	0.818	0.500	1				
	p	0.000	0.000	0.000	0.000	0.000	0.000					
Energy/fatigue	r	0.643	0.665	0.476	0.499	0.801	0.505	0.751	1			
	p	0.000	0.000	0.000	0.000	0.000	0.000	0.000				
Effects of nephropathy	r	0.661	0.528	0.420	0.492	0.728	0.449	0.625	0.695	1		
	p	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000			
Burden of nephropathy	r	0.626	0.594	0.569	0.674	0.789	0.470	0.796	0.719	0.671	1	
	p	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000		
Symptoms – problems	r	0.591	0.675	0.535	0.549	0.684	0.433	0.652	0.771	0.640	0.620	1
	p	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	

PF Physical function, *PR* physical role, *EWB* emotional well-being, *ER* emotional role, *SF* social function, *E/F* energy/fatigue

Table 5 Pearson analysis for patients' dimensions of sleep

Factors	Global PSQI score	Subjective sleep quality	Sleep latency	Sleep duration	Habitual sleep efficiency	Sleep disturbances	Use of sleeping medication	Daytime dysfunction
Global PSQI score	1	0.711**	0.681**	0.571**	0.455**	0.624**	0.289	0.581**
Subjective sleep quality	0.711**	1	0.944**	0.312*	0.380*	0.563**	0.231	0.495**
Sleep latency	0.681**	0.944**	1	0.332*	0.364*	0.551**	0.134	0.506**
Sleep duration	0.571**	0.312*	0.332*	1	0.571**	0.400**	−0.038	0.143
Habitual sleep efficiency	0.455**	0.380*	0.364*	0.571**	1	0.227	−0.151	0.134
Sleep disturbances	0.624**	0.563**	0.551**	0.400**	0.227	1	0.260	0.623**
Use of sleeping medication	0.289	0.231	0.134	−0.038	−0.151	0.260	1	0.318*
Daytime dysfunction	0.581*	0.495*	0.506**	0.143	0.134	0.623**	0.318*	1

*$p < 0.05$, **$p < 0.0001$

sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction.

4 Discussion

The results of KDQoL scores show a significant effect of CKD-FS in HRQOL of the patients who participated in the study. The score of the HRQOL is very low, 36.86 ± 11.95 and 39.87 ± 12.44 for total physical and mental health, respectively. General health follows (33.57), while all dimensions of emotional and physical well-being are low (<60). Overall health shows a strong correlation with emotional well-being and physical function (0.742 and 0.730, respectively). Strong correlation was found, in descending order, in the effects of nephropathy, energy, social function, the burden of nephropathy, and the emotional role. The pain, the symptoms of the disease, and the physical role were found to have moderate correlation.

Physical health outcomes are in line with the findings of the Dialysis Outcomes and Practice Patterns Study (DOPPS) for the whole sample and the whole of Europe (35.3 and 35.5, respectively), slightly higher than the United States (32.7) and lower than Japan (41.5). In terms of mental health, the results of our study are lower than the corresponding values (total, 44.9; Europe, 42.7; United States, 44.5; Japan, 46.5) (Mapes et al. 2003). The classification of the symptoms of the disease found in our study is in accordance with findings in the development of KDQOL, where the loss of energy, the limitation of physical abilities and the lifting of objects, and the limitations on fluids and nutrition significantly annoy patients (Hays et al. 1994). A study compared the two editions of KDQOL and their relevance to the Chinese population and showed similar results to the two basic dimensions (physical health, 36.27; and mental health, 41.12) in the same group (KDQOL-SFTM) (Chow and Tam 2014).

Sleep is a parameter that is related both to the physical and mental dimension of HRQOL. The quality of the participants' sleep is decreased, both in KDQOL and PSQI. The correlations of dimensions with each other and the overall quality of sleep show that the total score is strongly correlated with subjective sleep quality ($r = 0.711$), sleep latency ($r = 0.681$), and sleep disturbances ($r = 0.624$). Moderate correlation shows the components of daytime dysfunction ($r = 0.581$), sleep duration ($r = 0.571$), and habitual sleep efficiency ($r = 0.455$). The self-assessment of sleep quality is almost completely related to sleep latency ($r = 0.944$). The decrease of sleep quality in hemodialysis patients is supported by the findings of several studies. A study in Hong Kong recorded low-quality sleep in all dimensions with a total grade of 8.5 ± 4.61 (Wang et al. 2016). Another study using the Athens Insomnia Scale (AIS) found poor sleep quality in both hemodialysis and transplant patients (Liaveri et al. 2017). Maung et al. (2017) in the United States, using the same tool, in 69 hemodialysis patients, recorded poor quality of sleep, with total PSQI score similar to our study (6.4 ± 4.3). Finally, Elder et al. (2008) performed a sleep quality assessment as part of the Dialysis Outcomes and Practice Patterns Study (DOPPS)

(1996–2001) in which they collected data from 11,351 patients in 308 hemodialysis units in seven countries, and 49% of the population reported poor sleep quality, with wide variation between countries (from 4.9 in Germany to 6.5 in Japan).

4.1 Limitations

The limitations of the present study are the small number of women in the study population and the fact that the nationality in both groups was limited to Greek. These facts prevent the investigation of correlations between various research parameters and especially demographic and personal data referring to similar studies.

5 Conclusions

The evolution of biomedical technology and science has greatly improved the life expectancy of patients with CKD and their clinical symptoms. At the same time, this improvement has a positive impact on the social support and interaction of patients where the contribution of the health-care professionals of hemodialysis units is important.

In spite of these positive findings, the quality of life of hemodialysis patients with CKD-FS remains poor, interfering with important functions such as sleep, vitality, cognition, and sexual function. Continuous and regular assessment of the quality of life of these patients and their satisfaction with medical and social services will help further the development of appropriate and effective institutional interventions at regional and national level, which can contribute significantly not only to improving the treatment of the disease but also to the overall improvement of physical, mental, and social well-being.

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Subjective Quality of Life, Religiousness, and Spiritual Experience in Greek Orthodox Christians: Data from Healthy Aging and Patients with Cardiovascular Disease

Konstantinos Giannoulis and Vaitsa Giannouli

1 Introduction

Spirituality and religiousness are increasingly gaining attention as old-age research variables especially relating to health and healthcare (Miller and Thoresen 2003). Connection with the divine or transcendent is important both in Eastern and Western traditions and in people's notions of spirituality (Underwood 2006). Different features of national cultural contexts have been found to strengthen or attenuate the relationship of religion and spirituality with subjective well-being (Bond et al. 2012; Diener et al. 2011; Eichhorn 2011).

Unfortunately, until now, no research related to spirituality and religiousness in healthcare is examining Greek Orthodox Christian younger and older adults (Giannouli 2017a, b). The aim of the present study is to compare older and younger Orthodox Christian adults regarding their spirituality and religiousness during a period characterized as financial crisis in Greece and secondarily to explore whether the existence of serious health problems such as the diagnosis of cardiovascular disease differentiates self-reported religiousness, spirituality, and life satisfaction in Greek Orthodox Christian elders.

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2 Methods

2.1 Participants

Two hundred and forty healthy young individuals (Mage = 28.63, SDage = 9.02; Meducation = 14.39, SDeducation = 1.64) and two hundred and twenty-seven healthy older adults (Mage = 72.23, SDage = 6.57; Meducation = 7.81, SDeducation = 3.93) from two cities (an urban center in Southern Greece and a less urbanized city in Northern Greece) participated in this study voluntarily during 2012–2016.

There were more female (53.6%, n = 268) than male participants (n = 199). About 44.4% (n = 222) participants of our sample were married or in a relationship and living with their partner. 244% (n = 48.8) were single or widowed and living alone. 29.8% (n = 149) of the participants reported themselves to be employed. In our sample, there were non-active church members (n = 213) and active church members (n = 254). Based on the educational level, the participants were grouped so as to reflect school requirements in Greece: compulsory education 1–9 years (n = 165), high school 10–12 years (n = 83), and any university level education 13+ years (n = 219). Their socioeconomic class was indicated by themselves based on their financial income as upper (n = 171), middle (n = 234), and lower (n = 62). Volunteers were recruited from a variety of sources (older participants at senior centers and retirement homes and younger participants mainly after university classes and at youth centers).

All participants gave informed consent and were treated according to the Declaration of Helsinki. The young and old adults had no past or current psychiatric diagnosis or cognitive deficits. Although some older adults had been following medication related mainly to various minor health problems, they had no official diagnosis of a cognitive deficit or other conditions and had scored above 27 points on the Greek version of the Mini-Mental State Examination (MMSE) to exclude dementia and to ensure correct understanding and completion of the questionnaires. Additionally, the elders were examined with the Geriatric Depression Scale (GDS) for the detection of depressive symptomatology. Exclusion criteria for both groups of younger and older participants were a history of psychiatric, neurological, or substance abuse dependence and a history of head injury. Additionally, non-native speakers of the Greek language and non-Orthodox participants were excluded in the final sample.

In addition to the above, a third group of older nonhospitalized adults with an MMSE > 27, who had a diagnosis of cardiovascular disease (history of heart attack) and were being treated medically, were included (n = 32, Mage = 71.21, SDage = 6.37, Meducation = 8.90, SDeducation = 4.15, Myearsofdisease = 7.65, SDyearsofdisease = 2.10).

2.2 Measures and Procedure

Participants filled out a demographic questionnaire, and then they were asked to complete three questionnaires which were already validated and in Greek: (1) the Daily Spiritual Experience Scale which consists of 16 questions concerning how an individual experiences in daily life the existence of God ($\alpha = 0.870$ in our sample) (Underwood 2011; Underwood and Teresi 2002), (2) the Systems of Belief Inventory (SBI-15R) which consists of 15 questions regarding religiousness and spirituality ($\alpha = 0.880$ in our sample) (Holland et al. 1998), and (3) the Satisfaction with Life Scale (SWLS) ($\alpha = 0.892$ in our sample), which is a 5-item measure that is widely used in research for the assessment of life satisfaction (as a global cognitive judgment of one's own life) and which has been used to measure the subjective quality of life of people experiencing serious health concerns (Diener et al. 1985). The religious identity of the participants was measured with the question: Are you a member of the Greek Orthodox Christian church? The measure was coded in a 3-point scale represented by (1) being an inactive member of the Greek Orthodox Christian church, (2) being an active member, and (3) not belonging to the Greek Orthodox Christian church (those participants were excluded) in the current analysis. The existence of a social network apart from the relevant questions (marital status) was also examined with a yes-no question: "Do you believe that you have a strong social network?" And the opinion about the current socioeconomic situation in Greece was measured with the question: Are you satisfied with the current socioeconomic situation in Greece? All elders were also examined after the questionnaire completion with MMSE. The survey took approximately 1 h to complete, and the responders completed all three questionnaires individually and anonymously.

3 Results

Results revealed that there are no statistically significant differences between the healthy younger and the older Greek Orthodox Christians regarding their spiritual experiences ($t(465) = 1.04$, $p = 0.297$), their religiosity ($t(464) = 1.415$, $p = 0.158$), and their life satisfaction ($t(465) = 0.490$, $p = 0.625$). The younger adults showed a slightly nonsignificantly lower score ($M = 47.62$, SD = 10.71) on Daily Spiritual Experience Scale in contrast to older adults ($M = 48.61$, SD = 9.72). A similar nonsignificant pattern was found for the Systems of Belief Inventory, with the younger adults showing lower scores ($M = 29.01$, SD = 8.06) in comparison to the older adults ($M = 30.21$, SD = 9.09). Life satisfaction was higher in a statistically nonsignificant way in younger individuals ($M = 15.55$, SD = 4.31) compared to older adults ($M = 15.34$, SD = 4.59). When the factor of educational level was examined, one-way analysis variance revealed no significant differences for the Daily Spiritual Experience Scale ($F(2, 464) = 1.487$, $p = 0.227$), the Systems of Belief Inventory

($F(2, 463) = 1.185$, $p = 0.307$), and the Satisfaction with Life Scale ($F(2, 464) = 0.971$, $p = 0.379$) regarding the different educational groups.

No statistically significant differences were found for the urban versus nonurban place of living for the Daily Spiritual Experience Scale ($t(464) = 0.124$, $p = 0.901$), the Systems of Belief Inventory ($t(463) = 1.472$, $p = 0.142$), as well as the Satisfaction with Life Scale ($t(464) = 1.465$, $p = 0.144$). When the participants were grouped according to their marital status, there was no statistically significant difference for the Daily Spiritual Experience Scale ($t(464) = 0.254$, $p = 0.8000$) and the Satisfaction with Life Scale ($t(464) = 1.794$, $p = 0.073$), but there was a statistical difference for the Systems of Belief Inventory ($t(463) = 2.298$, $p = 0.022$) with the participants who were married or living with a partner having higher reported scores ($M = 30.51$, SD = 8.83) in contrast to the participants who didn't live with a partner ($M = 28.68$, SD = 8.83).

The grouping of participants according to their employment status (employed-unemployed) again showed no differences for the Daily Spiritual Experience Scale ($t(465) = 0.584$, $p = 0.560$), the Systems of Belief Inventory ($t(464) = 1.029$, $p = 0.304$), and the Satisfaction with Life Scale ($t(464) = 0.104$, $p = 0.917$). Grouping according to the socioeconomic status as indicated by the participants showed no differences for the Daily Spiritual Experience Scale ($F(2, 464) = 0.712$, $p = 0.491$), the Systems of Belief Inventory ($F(2, 463) = 2.874$, $p = 0.057$), and the Satisfaction with Life Scale ($F(2, 464) = 0.159$, $p = 0.853$). Grouping according to the decade of life for the healthy elders (54–64, 65–75, 76–86 years) revealed no statistically significant differences in life satisfaction ($F(2, 224) = 0.009$, $p = 0.991$), religiousness ($F(2, 224) = 1.866$, $p = 0.157$), and spirituality ($F(2, 224) = 2.367$, $p = 0.096$).

Multiple regression analyses, including marital and employment status, gender, age, socioeconomic status, education, urbanicity, degree of church membership, existence of social network, personal beliefs about the country's socioeconomic situation, and depression, revealed that some of the above are predictors of religiousness, spirituality, and life satisfaction (Tables 1 and 2).

A moderate correlation between the Daily Spiritual Experience Scale and the Systems of Belief Inventory (SBI-15R) ($r = 0.415$, $p < 0.001$) was found, but also a slightly negative relationship between the Systems of Belief Inventory and Satisfaction with Life Scale was reported ($r = -0.113$, $p = 0.015$). The only statistically significant difference between older and younger healthy adults is the degree of being an active church member ($t(465) = 5.041$, $p < 001$), as younger adults reported less involvement ($M = 1.34$, SD = 0.47) in comparison to older adults ($M = 1.57$, SD = 0.49).

Finally, there were no statistically significant differences between elder patients with a diagnosis of cardiovascular disease and healthy elder controls matched exactly on sex, years of education, and age for the Daily Spiritual Experience Scale ($t(62) = 0.773$, $p = 0.442$), the Systems of Belief Inventory ($t(62) = 0.232$, $p = 0.818$), and the Satisfaction with Life Scale ($t(62) = 0.575$, $p = 0.567$).

Table 1 Regression analyses for the contribution of predictors regarding quality of life-life satisfaction, religiousness, and spirituality in the sample of healthy participants ($n = 467$)

Independent variables	Dependent factor	*B*	*t*	*p*	R^2
Systems of Belief Inventory	Daily Spiritual Experience Scale	0.520	9.980	0.000	0.187
Marital status	Systems of Belief Inventory	−5.949	−3.600	0.000	0.232
Employment status		2.982	2.572	0.010	
Age group (young, old)		1.969	2.257	0.024	
Belief about the country's situation		1.784	2.069	0.039	
Daily Spiritual Experience Scale		0.344	9.980	0.000	
Satisfaction with Life Scale		−0.232	−2.898	0.004	
Marital status	Satisfaction with Life Scale	−2.202	−2.278	0.023	0.035
Employment		1.152	2.256	0.025	
Systems of Belief Inventory		−0.078	−2.898	0.004	

Table 2 Regression analyses for the contribution of predictors regarding quality of life-life satisfaction, religiousness, and spirituality in the sample of healthy younger participants, healthy older participants, and older patients suffering from cardiovascular disease

Independent variables	Dependent factor	*B*	*t*	*p*	R^2
Healthy older adults (n = 227)					
Systems of Belief Inventory	Daily Spiritual Experience Scale	0.275	3.994	0.000	0.108
Active church membership	Systems of Belief Inventory	9.186	2.781	0.006	0.182
Gender		−8.220	−2.269	0.024	
Marital status		−4.370	−3.260	0.001	
Satisfaction with Life Scale		−0.434	−3.456	0.001	
Daily Spiritual Experience Scale		0.235	3.994	0.000	
Employment status	Satisfaction with Life Scale	1.829	2.126	0.035	0.096
Marital status		−1.154	−2.157	0.032	
Systems of Belief Inventory		−0.122	−3.456		
Healthy younger adults (n = 240)					
Systems of Belief Inventory	Daily Spiritual Experience Scale	0.785	10.534	0.000	0.336
Beliefs about the Greek socioeconomic situation	Systems of Belief Inventory	2.596	2.186	0.030	0.380
Daily Spiritual Experience Scale		0.415	10.534	0.000	
Age in years	Satisfaction with Life Scale	−0.093	−2.870	0.004	0.050
Older patients with cardiovascular disease (n = 32)					
Marital status	Satisfaction with Life Scale	2.797	2.192	0.040	0.100 (R adjusted)

4 Discussion

Not in line with previous studies from other countries, the Greek older and younger adults do not have high scores on self-reported religiousness and spirituality, a finding that may be influenced by the current socioeconomic environment in Greece. Additionally, the finding of similar responses in spirituality, religiousness, and quality of life-life satisfaction in older adults with cardiovascular disease and healthy elders is in contrast with the finding that people may have greater spiritual needs during illness as seen in studies in non-Greek Orthodox Christians (Powell et al. 2003; Westlake and Dracup 2001) and may indicate that other factors apart from disease may play a significant role (Beery et al. 2002).

The moderate correlation between the Systems of Belief Inventory and the Daily Spiritual Experience Scale reveals that there is a positive relation between spirituality and religiousness and that these two constructs are distinct (Lucchetti et al. 2015). The unexpected finding of a slightly negative relationship between the Systems of Belief Inventory and Satisfaction with Life Scale and the absence of satisfactorily demographic predictors on spirituality, religiousness, and quality of life-life satisfaction may be due to the new unprecedented socioeconomic changes that have been in action in Greece since 2009. In general, people who score low on Satisfaction with Life Scale (young: $M = 15.55$, SD = 4.31; and old: $M = 15.34$, SD = 4.59) usually have small but significant problems in several areas of their lives or have many areas that are doing fine but one area that represents a substantial problem for them. The above findings may improve the understanding of practicing clinicians regarding elders' quality of life and depression in the Greek healthcare system. Of course, the above findings should be further investigated as participants from different cultural or faith backgrounds may differ in their understanding of the items pertaining to spiritual experience and religiousness (Chen et al. 2011; Stoyanova et al. 2017).

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Mini-Mental State Examination: Greek Normative Data Stratified by Age and Education in a Large Sample of 925 Community-Dwelling Healthy Participants

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1 Introduction

The understanding of cognitive changes that accompany aging is of paramount importance not only because better cognitive function is associated with higher levels of psychological well-being in community living older adults (Llewellyn et al. 2008) but also because cognitive changes affect older adults' daily function and also enable the distinction between normal and pathological states (Salthouse 2012). Cognitive screening measures are widely administered in everyday clinical practice in different geriatric settings (Sheehan 2012). Despite the presence of several extended-like screening tests, Mini-Mental State Examination (MMSE) (Folstein et al. 1975, 1983) continues to be largely used not only by neuropsychologists, neurologists, and psychiatrists but also by general practitioners and other health-related specialties and is often the subject's "cognitive-identity" marker when clinicians discuss about patients' cognitive status and the need for further neuropsychological evaluation arises. Although a cutoff score (i.e., 23/24, 24, or even 20/21), which constitutes a significant methodological tool in clinical and research practice, is usually applied (Anthony et al. 1982; Levin et al. 1989; Roth et al. 1988), the effect of demographic characteristics is often ignored. However, normative data based on the effect of age, education, and/or gender significantly contribute to a more sensitive and specific identification of impaired performance even in cognitive screening measures (Strauss et al. 2006).

The aim of the present study was to improve the available data regarding a single cutoff score and provide normative data for the MMSE in a large sample of

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community-dwelling healthy participants aged over 50 years old stratified based on the effects of demographic characteristics and using the methodological advantage of overlapping cell procedure.

2 Materials and Methods

2.1 Participants

This cross-sectional study was conducted on six municipalities of Attica prefecture (e.g., Petroupoli, Aigaleo, Nea Philadelphia, Kifissia, Vrilissia, Korydallos) on community-dwelling adults. A total of 1030 participants aged ≥50 years old were initially enrolled in the study. Informed consent was obtained from all participants of the study which was conducted in accordance with the Declaration of Helsinki and its later amendments and had been approved by the Local Ethical Committee of the "Nestor" Psychogeriatric Association. Inclusion criteria were age > 50 years, education >1 year and ability to read and write in Greek, available data (i.e., Geriatric Depression Scale, GDS; Yesavage 1992) for depression and GDS score < 11, absence of neurological or severe psychiatric disorders, absence of severe uncontrollable organic diseases (including cerebrovascular or metabolic diseases), normal performance (>9th percentile) in other cognitive measures (e.g., Trail Making Test, Rey Auditory Verbal Learning Test, Verbal Fluency), absence of sensorimotor deficits that did not allow test administration, and absence of severely affected daily living functions based on self-reports. The final sample included 925 participants of both genders.

2.2 Cognitive Testing

A clinical history was obtained for all subjects to evaluate whether they were suitable to be included in the study. The GDS was administered in order to evaluate participants' mood status and excluded subjects with significant evidence of depressive symptomatology (GDS ≥ 11). All participants administered the MMSE as it is provided in Strauss et al. (2006) based on formal instructions. The total score was calculated for further analysis.

2.3 Statistical Analysis

Continuous variables are presented as mean ± standard deviation (SD), while categorical variables are presented as frequencies. Normality assumptions were tested with skewness, kurtosis, and Q-Q plots before further analysis. The association

between age, education, GDS, and MMSE total score was tested using correlation analysis (Pearson's r). Between-group differences (i.e., gender effect) were evaluated using t-test for independent samples. The contribution of demographic characteristics on MMSE total score was evaluated using hierarchical regression analysis. The sample was divided into seven overlapping age tables with midpoints at 55, 60, 65, 70, 75, 80, and 85 years using the overlapping cell procedure which increases both the accuracy and the clinical utility of the data (Pauker 1988).

Normative data were thus calculated for seven midpoint age groups (i.e., 50–60, 55–65, 60–70, 65–75, 70–80, 75–85, 85–91) as Table 2 show. Each age group was stratified into four educational groups (i.e., 1–5, 6–9, 10–12, 13–16 years) which correspond to the national educational system for illiteracy/incomplete compulsory education (1–5), lower and higher compulsory education (6–9 and 10–12, respectively), as well as tertiary education (13–16). To interpret the MMSE total score, the clinicians will select the table with the closest midpoint to the subject's age and then select the appropriate educational group. Each table shows the mean and SD and representative percentiles which correspond to Z-scores of −2.00 (2nd %ile), −1.66 (3rd %ile), −1.33 (9th %ile), −1.00 (16th %ile), −0.66 (25th %ile), −0.33 (37th %ile), 0.00 (50th %ile), 0.33 (63rd %ile), 0.66 (75th %ile), 1.00 (84th %ile), 1.66 (95th %ile), and 2.33 (99th %ile). Scores for each percentile were automatically calculated using the statistical software. The level of statistical significance was set at $p < 0.05$, and all analyses were conducted using IBM SPSS v. 20.0.

3 Results

Table 1 presents the demographic characteristics from the sample of 925 healthy participants as well as descriptive measures for the MMSE total score separately for each age group, for males and for females, as well as for each education group.

Correlation analysis revealed a significant association between MMSE total score and age ($r = -0.384$; $p < 0.001$) (Fig. 1a) and total score and education ($r = 0.416$; $p < 0.001$) (Fig. 1b). Increased age and lower educational level were associated with decreased scores in MMSE. There were no gender effects ($t = -0.582$; $p > 0.05$, ns).

Based on the initial correlation analysis and between-group t-test, age and education were entered into a regression analysis model. Hierarchical regression analysis revealed that education significantly accounted for 17.3% of the total variance in the MMSE total score with age adding a significant 7.4% to the final model (adjusted $R^2 = 0.246$, $F = 151.872$, $p < 0.001$; age: $\beta = -0.286$, $p < 0.001$; education: $\beta = 0.332$, $p < 0.001$).

Normative data (mean, SD, percentile scores) for the MMSE total scores are shown in Table 2. The sample size and the gender distribution within each group (age per education) are also provided.

Table 1 Demographic characteristics and descriptive measures of the total sample of 925 community-dwelling healthy participants based on age, gender, and education

Demographic variables	*N*	Age		MMSE total score	
		Mean	SD	Mean	SD
Age (yrs)					
50–60 (midpoint: 55)	161	56.68	2.88	28.06	1.51
55–65 (midpoint: 60)	319	61.11	2.96	27.95	1.66
60–70 (midpoint: 65)	452	65.50	3.07	27.75	1.84
65–75 (midpoint: 70)	430	69.44	2.95	27.45	1.97
70–80 (midpoint: 75)	307	73.92	3.21	26.82	2.20
75–85 (midpoint: 80)	195	79.21	2.94	25.97	2.30
80–91 (midpoint: 85)	109	82.88	2.77	25.49	2.41
Gender					
Male	231	71.53	8.32	27.23	2.09
Female	694	67.34	7.94	27.32	2.11
Education (yrs)					
1–5	40	76.98	5.74	24.03	2.63
6–9	363	70.23	7.73	26.67	2.09
10–12	241	66.87	7.97	27.77	1.72
13–16	281	66.08	8.08	28.17	1.58

Note: *MMSE* Mini-Mental State Examination, *yrs* years

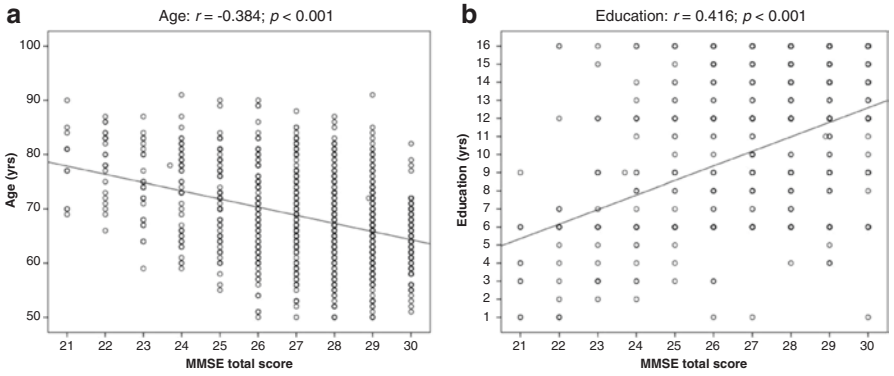

Fig. 1 Scatterplots for the correlation between MMSE total score and age (**a**) and education (**b**)

4 Discussion

The aim of the present study was to provide normative data for a large sample of community-dwelling healthy participants for the most commonly used cognitive screening measure in order to increase its usefulness, specifically in everyday clinical practice.

In the present study, we found a significant association between age, education, and total MMSE score with older and less educated participants having lower

Table 2 Normative data for the total MMSE score for each age group (midpoints: 55, 60, 65, 70, 75, 80, 85) stratified into four educational groups (1–16)

	Age group: 50–60 (midpoint: 55)			
	Education group			
Age/education group	1–5	6–9	10–12	13–16
N	–	36	56	7/62
M/F	–	3/33	6/50	69
MMSE (mean ± SD)	–	27.36 ± 1.73	28.13 ± 1.55	28.38 ± 1.23
Percentile				
2nd	–	24	23	25
3rd	–	24	24	26
9th	–	25	26	26
16th	–	25	27	27
25th	–	26	27	28
37th	–	27	28	28
50th	–	28	29	29
63rd	–	28	29	29
75th	–	29	29	29
84th	–	29	30	30
95th	–	30	30	30
99th	–	–	–	–

	Age group: 55–65 (midpoint: 60)			
	Education group			
Age/education group	1–5	6–9	10–12	13–16
N	–	100	101	118
M/F	–	17/83	17/84	26/92
MMSE (mean ± SD)	–	27.21 ± 1.71	28.15 ± 1.70	28.41 ± 1.33
Percentile				
2nd	–	23	24	25
3rd	–	24	24	26
9th	–	25	25	26
16th	–	25	26	27
25th	–	26	27	28
37th	–	27	28	28
50th	–	27	29	29
63rd	–	28	29	29
75th	–	28	29	29
84th	–	29	30	30
95th	–	30	30	30
99th	–	30	30	30

	Age group: 60–70 (midpoint: 65)			
	Education group			
Age/education group	1–5	6–9	10–12	13–16
N	5	179	123	145
M/F	0/5	27/152	29/94	41/104

(continued)

Table 2 (continued)

	Age group: 60–70 (midpoint: 65)			
	Education group			
Age/education group	1–5	6–9	10–12	13–16
MMSE (mean ± SD)	23.00 ± 2.12	27.15 ± 1.84	27.99 ± 1.69	28.45 ± 1.45
Percentile				
2nd	21	23	24	24
3rd	21	23	24	25
9th	21	25	25	26
16th	21	25	26	27
25th	21	26	27	28
37th	21	27	28	28
50th	23	27	28	29
63rd	24	28	29	29
75th	25	29	29	29
84th	–	29	30	30
95th	–	30	30	30
99th	–	30	30	30

	Age group: 65–75 (midpoint: 70)			
	Education group			
Age/education group	1–5	6–9	10–12	13–16
N	16	185	108	121
M/F	0/16	36/149	22/86	43/78
MMSE (mean ± SD)	24.56 ± 2.90	26.95 ± 1.96	27.81 ± 1.61	28.28 ± 1.54
Percentile				
2nd	21	22	24	23
3rd	21	22	24	24
9th	21	24	26	26
16th	22	25	26	27
25th	23	26	27	28
37th	23	27	27	28
50th	24	27	28	29
63rd	24	28	29	29
75th	28	28	29	29
84th	29	29	29	30
95th	–	30	30	30
99th	–	30	30	30

	Age group: 70–80 (midpoint: 75)			
	Education group			
Age/education group	1–5	6–9	10–12	13–16
N	27	138	70	72
M/F	2/25	42/96	24/46	31/41
MMSE (mean ± SD)	24.59 ± 2.82	26.43 ± 2.13	27.36 ± 1.71	27.89 ± 1.66

(continued)

Table 2 (continued)

	Age group: 70–80 (midpoint: 75)			
	Education group			
Age/education group	1–5	6–9	10–12	13–16
Percentile				
2nd	21	22	23	24
3rd	21	22	24	24
9th	21	23	25	25
16th	22	24	26	26
25th	22	25	26	27
37th	23	26	27	28
50th	24	27	28	28
63rd	25	27	28	29
75th	27	28	29	29
84th	29	29	29	29
95th	30	30	30	30
99th	–	30	–	–

	Age group: 75–85 (midpoint: 80)			
	Education group			
Age/education group	1–5	6–9	10–12	13–16
N	22	97	37	39
M/F	2/20	39/61	18/19	20/19
MMSE (mean ± SD)	23.86 ± 2.44	25.65 ± 2.28	26.95 ± 1.62	27.05 ± 1.79
Percentile				
2nd	21	21	23	23
3rd	21	21	23	23
9th	21	22	24	24
16th	22	23	25	25
25th	22	24	26	26
37th	22	25	27	27
50th	24	26	27	27
63rd	25	27	28	28
75th	25	27	28	28
84th	26	28	29	29
95th	30	29	29	30
99th	–	–	–	–

	Age group: 80–91 (midpoint: 85)			
	Education group			
Age/education group	1–5	6–9	10–12	13–16
N	14	55	19	21
M/F	3/11	20/35	9/10	11/10
MMSE (mean ± SD)	23.00 ± 1.92	25.33 ± 2.33	26.47 ± 1.87	26.67 ± 2.11

(continued)

Table 2 (continued)

	Age group: 80–91 (midpoint: 85)			
	Education group			
Age/education group	1–5	6–9	10–12	13–16
Percentile				
2nd	21	21	22	22
3rd	21	21	22	22
9th	21	22	23	23
16th	21	23	24	24
25th	22	24	25	26
37th	22	25	27	26
50th	22	25	27	27
63rd	23	26	27	28
75th	24	27	28	28
84th	26	28	28	29
95th	–	29	–	30
99th	–	–	–	–

Note: *MMSE* Mini-Mental State Examination, *M/F* male/female, *SD* standard deviation

performance in MMSE. Our results corroborate previous findings regarding the effect of age and education on MMSE scores (for a comprehensive review, see Strauss et al. 2006). Similar effects have been reported in non-English-speaking populations as well (e.g., Italy, Finland, Brazil, Korea, Japan) (Steis and Schrauf 2009). The absence of gender effects in the present study is not surprising since it seems that gender has little impact on the MMSE total score (Strauss et al. 2006).

Several cognitive screening measures either for the general population (e.g., ACE-R; Mioshi et al. 2006) or specific clinical groups (i.e., Parkinson's disease: PDCRS; Pagonabarraga et al. 2008; Motor Neuron Disease: ECAS; Abrahams et al. 2014) have been constructed as initial screening procedures to characterize subjects' cognitive status at baseline, evaluate cognitive changes in follow-up examinations, identify issues related to pharmacological and non-pharmacological treatment interventions, and undoubtedly refer for further comprehensive neuropsychological evaluation. However, it seems that the MMSE continues to be the subject's "cognitive-identity" marker, specifically in routine clinical practice, by either experienced or non-experienced clinicians to initially rule out a diagnosis of dementia (Mitchell 2009). Even though there is no doubt that its use is not without limitations (Wind et al. 1997), the clinical utility of this cognitive screening measure may be improved through awareness of the influences of demographic variables (Tangalos et al. 1996). Despite the presence of widely accepted and used cutoff score for the MMSE which also applies for the Greek population (Fountoulakis et al. 2000; Solias et al. 2014), the use of normative data for different age and education groups may increase the usefulness of this cognitive screening measure.

The latter becomes more important in Greece considering the National Action Plan for Dementia-Alzheimer's Disease and the establishment of memory clinics in

several public hospitals where the use of short screening tests such as the MMSE might be inevitable. We herein applied the overlapping cell procedure to stratify our sample in different age groups. According to Pauker (1988), the use of overlapping cell procedure is "a way to resolve the conflict between (1) constructing norm tables that have a relatively large *N* in each subcategory cell, but for which the limited total sample size limits the number of cells and dictates for each cell a very wide range of the modifier variables; and (2) constructing norm tables in which the ranges of the modifier variables are narrower, but for which the limited total sample size severely limits the size of the *N* for each cell." The initial large sample size of our study and the use of overlapping cell procedure result in normative tables that provide direct comparisons with MMSE scores of healthy participants who surround specified age-by-education reference points.

Strengths of the present study include the large sample size aged between 50 and 91 years old of both genders and with a wide range of years of education, the methodological approach of overlapping cell procedure, and the presentation of percentile scores for each stratified group. However, our study is not without limitations which include the absence of participants living outside of Attica prefecture and the absence of clinical samples to further provide sensitivity and specificity values within each normative group.

In conclusion, current normative data for the Greek version of the MMSE with age- and education-related stratification in a large sample of 925 healthy participants are provided as a useful set of norms for clinical and research practice.

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Conflicts of Interest There are no conflicts of interest.

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The Role of the Family in the Care of Alzheimer Patients

Florou Xristina, Kalatzi Demeter, Gripiotis John, and Chania Maria

1 Introduction

According to the World Health Organisation, people's life expectancy worldwide is continuously growing, and on the one hand, that is one of the greatest triumphs of humanity to date. But at the same time, it is also one of the most important challenges as the aging of the population raises economic and social requirements in all countries.

By 2025, the number of people over 60 will have increased by 250%, and by 2050, this figure will have reached 2 billion, thus replacing the triangular population pyramid with a more cylindrical structure. As a result, one-third of the population of a country is made up of people over 60, mainly in countries such as Italy, Germany, Japan and Greece. The United States and Canada are also in the same situation. Europe is experiencing a particular problem with the "Euro-aging" phenomenon since the combination of low birth rates and the increase in European citizens' life expectancy constitute a major social, economic and public health problem.

Social development, improved living conditions and medical progress lead to the conclusion that more people have the opportunity to live longer than in the past. The aging population is a particular feature of demographic trends in developed countries. This trend is closely linked to the growing number of diseases in old age and the increase in government spending on health and social care. One of the most commonly reported diseases related to old age is reported to be dementia. The cause

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may lie in any kind of illness, the most common being Alzheimer's disease and cerebrovascular disease. It should be noted that the care of 35 million patients suffering from dementia costs over 600 billion dollars a year; that is about 1% of the world's Gross Domestic Product (Marešová et al. 2015). Thus, it should be noted that the cost of dementia is greater than that of national and international priority diseases such as HIV, cancer, heart disease, stroke and diabetes. On the basis of simple demographic data, the cost of dementia is predicted to increase by 85% by 2030, while developing countries will have an increased share of the economic burden (Banerjee 2012).

It is estimated that 24 million people worldwide suffer from dementia, the majority of whom are believed to suffer from Alzheimer's disease (AD). So AD represents an important public health issue and has been recognised as a research priority (Ballard et al. 2011).

2 Historical Retrospection of Alzheimer's Disease

German psychiatrist Lois Alzheimer was the first who presented the case of a 51-year-old woman who developed a paranoid ideation and subsequent speech disorders in 1907. Post-mortem examination of the brain revealed cerebral cortex atrophy and significant changes that he described as senile plaques and neurofibrillary lesions. Two years after Alzheimer's announcement, Charles Ladame, an assistant at the Geneva Psychiatric Hospital, studied approximately 100 brains of dementia patients under the microscope and briefly described the cortical lesions of senile dementia. The disease was considered rare, and by the year 1960, about 100 publications were reported in literature. In the 1960s, pioneering studies conducted in Newcastle, England, by Blessed, Tomlinson and Roth showed that there was a link between the number of senile plaques in the cerebral cortex and the severity of mental deficiency while there was no difference between senile and presenile cases (Mentenopoulos and Mpouras 2002).

3 Family and AD Patients

3.1 The Role of the Family

Many dementia patients depend on a family member for help. Caring for nonautonomous individuals, such as those with dementia, causes discomfort (Raggi et al. 2015). The caregivers of the family face challenges in their orientation after the onset of Alzheimer's disease in their family members. Their personal environment, the family cohesion and the perception of the future change successively as they face multiple challenges in the process of becoming caregivers (Välimäki et al.

2012). At the same time, they also face many adverse effects on physical and mental health, as well as economic repercussions (Nguyen 2009).

Worldwide, the biggest burden of caring for elderly patients with dementia is taken on by the family, which is the cornerstone of care for these people. As the needs and requirements of the patient grow or intensify, first-rate family caregivers respond by implementing strategies that reduce the burden of care. Those who are unable to adapt or modify strategies to meet the demands of care experience high levels of burden and psychiatric morbidity. Supporting the family in the work of care, identifying the factors that predispose a burden and avoiding the creation of "hidden patients" are key tasks and challenges for nurses around the world and Cyprus in particular (Papastavrou 2005).

Nevertheless, an effort is made to keep the individual in his/her home, in a familiar environment, in the environment where he/she will have increased chances of remaining calm. Although it seems like a tragedy for many of those affected and especially for family members, pleasure, joy, love, affection and appreciation of enthusiasm, memory and beauty, especially love, as well as many other life-improving properties are still present from the patient and the family members. To achieve this, the family members must be well informed, skilled and, above all, well-rested and energetic if they plan on reducing the impact of Alzheimer's disease on the patient, the family and our society (Ham 1990).

Many researchers have identified the problems faced by caregivers of people with dementia. These include the real loss of companionship and the support of a life partner, social isolation and complex economic, legal and social decision-making. The burden of care is financially, emotionally and physically important as well (Thompson and Spilsbury 2007).

According to another survey, family members of a dementia patient often experience what was called the "caregiver's unexpected career" and face multifaceted, complex and stressful situations that can have significant consequences. This exploratory study was designed to address this major public health challenge through the lens of planned rest and caregivers' commitment. While many caregivers report gaining significant emotional and spiritual rewards from their role, many also face physical and emotional problems directly related to anxiety and the demands of daily care (Roberts and Struckmeyer 2018).

3.2 The Burden on the Family

Taking care of patients with Alzheimer's often leads to mental and physical health problems for these caregivers. Some factors predict the hardship of caregivers, such as the presence of patient behaviour problems due to illness, the social support of caregivers and the ability to cope with difficult situations. The term "caregiver's burden" is used to refer to the physical, psychological or emotional, social and economic problems faced by family members caring for elderly adults. Caregivers of

relatives suffering from Alzheimer's are extremely anxious and at risk of physical and psychiatric conditions (Cheng et al. 2012).

In the face of demographic changes, atypical care of patients with dementia is increasingly important. However, due to the symptoms of dementia and ongoing care requests, this subgroup of atypical caregivers faces a large number of stressors that cause chronic stress and impaired physical and mental health. Based on ongoing research on maintaining a healthy lifestyle despite anxiety and adversities, there is an increasing interest in identifying endurance factors that can serve to address the care and protection of caregivers of individuals with dementia in the near future (Scott et al. 2018).

According to a study conducted in Japan, which aimed at supporting people with dementia living alone through nursing interventions, caregivers have gained a deeper understanding of the disease and the suitable ways to care for dementia patients. In particular, caregivers perceived positive changes not only in themselves but also in their recipients such as improvements in symptoms and quality of life.

Finally, caregivers realised that people with dementia can live on their own if appropriate services are provided (Kitamura et al. 2019). Caring for a person who suffers from Alzheimer's disease and other forms of dementia is particularly challenging and affects every aspect of the life of family caregivers. Family care is defined as atypical, unpaid care provided by family or friends to people with chronic illness or disability (Raś and Opala 2015). At present, there are more than 15 million unpaid caregivers for people with Alzheimer's disease and dementia-related diseases. This unpaid care can be stressful for caregivers due to the chronic nature of the illness, as well as other factors (Llanque et al. 2016).

4 Conclusions

Caring for a dementia patient can be very difficult. However, there are always ways to deal with the situation. With Alzheimer's disease, the whole family suffers along with the patient. The high demands of the care for dementia patients affect the health of caregivers, influence their participation in social and professional activities, reduce their leisure time, undermine their social position and threaten their financial security. The most important burden, however, is the increased demand for care and the sense of guilt and fear of death that the caregiver feels. Understanding and accepting these feelings greatly facilitate his/her difficult task.

4.1 Proposals

1. It is necessary for the caregiver to take care of themselves.
2. The caregiver should seek help from other family members when it is available so as not to bear the burden of patient care alone.

3. They must share their concerns about patient care with other people.
4. The caregiver must make sure that they have free time for themselves in order to be able to care for the patient more effectively.
5. He/she must identify the limits of their mental and physical endurance.
6. Seeking help and advice about the disease of the person they are caring for is a prerequisite.
7. Remember that they are important and should take care of themselves.

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Prevalence of Stroke Cases in Warangal, Telangana Region, India: A Hospital-Based Case Study

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1 Introduction

Globally, stroke is the most common cause of mortality after coronary artery disease. The risk of stroke in elders aged >55 years is 1 in 6 for men and 1 in 5 for women (Seshadri et al. 2006). Moreover, stroke is becoming a main cause of early death and disability in developing countries like India, mostly enhanced by the increased predominance of major risk factors. According to World Health Organization (WHO), stroke accounts for 10.8% of mortality and 3.1% of disease burden worldwide. A recent review on the literature revealed that during the past decade in India, the cumulative incidence of stroke ranged from 105 to 152 per 1 lakh individuals per year, and the crude incidence of stroke ranged from 44.29 to 559 per 1 lakh individuals. These values were quite higher compared to the values of high-income countries (Kamalakannan et al. 2017). Stroke is a brain injury caused by a sudden interruption of oxygen-rich blood supply to the brain or hemorrhage in the blood vessels of the brain. According to WHO, stroke is clinically defined as "the rapid development of clinical signs and symptoms of a focal neurological trouble lasting more than 24 hours or leading to death with no apparent cause other than vascular origin" (Taylor and Suresh 2012). The major risk factors associated with stroke are high blood pressure, smoking, alcohol consumption, diabetes, obesity, physical inactivity, low fruit and vegetable consumption, etc.

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According to American Stroke Association, stroke is classified as ischemic (clots), hemorrhagic (bleeds), and TIA (transient ischemic attack). Ischemic stroke happens due to a blockade within a blood vessel supplying blood to the brain, and it accounts for 50–87% of all stroke cases. Hemorrhagic stroke occurs as a result of weakened blood vessel ruptures. The most common reason of hemorrhagic stroke is high blood pressure (uncontrolled hypertension). TIA (transient ischemic attack) is initiated by a temporary blood clot; it is also called a "ministroke." A population-based survey had identified prevalent stroke cases from a defined urban and rural area. The study revealed that the age-adjusted stroke prevalence was found higher in rural areas (165 per 1 lakh) compared to urban areas (136 per 1 lakh) (Gourie-Devi et al. 2004). The two Kolkata-based studies found an increasing trend in the incidence of stroke, with 262 per 1 lakh individuals affected in 1993 to 1995, 334 per 1 lakh individuals during 1999, and 545 per 1 lakh in 2005 (Banerjee et al. 2001; Das et al. 2007). A 2-year survey (2006–2008) was conducted by using the WHO screening tool at Dharavi (Mumbai) which revealed that the age-adjusted prevalence of stroke was 4.87 per 100 persons. The prevalence of stroke in men was 6.74 per 100 persons, which was nearly double compared to women (3.48 per 100 persons) (Mukhopadhyay et al. 2012). Hospital-based study conducted on stroke cases from different parts of India showed an increased incidence of stroke rate (Nagaraja et al. 2009; Sridharan et al. 2009; Pandian et al. 2015). However, existing figures on stroke prevalence in India include many methodological imperfections such as small sample sizes, unpredictable diagnostic criteria, and inappropriate survey approaches. Moreover, very limited studies were conducted in the context of habit-related risk factors (smoking/drinking) in stroke causation. Furthermore, no prior studies on stroke have been conducted from Telangana region; therefore, we conducted a systematic hospital-based study from Telangana region with our objectives being to investigate the incidence and to examine habit-associated risk factors and mortality rate of stroke in this part of country as well as to apprehend the real magnitude of this problem.

2 Materials and Methods

2.1 Data Collection

The present hospital-based study was conducted during the year 2014 and 2015. The study subjects comprised of the patients who were admitted to MGM Hospital. A district-level government hospital, MGM Hospital is a 1000-bed teaching hospital located in Warangal, Telangana region. There are patients admitted to the same hospital from other districts of Telangana region. Most of the critical cases taken up by other hospitals in Warangal are also transferred to MGM hospital. Total inpatient admissions to the hospital are around 500 per day. After resuscitation in emergency ward, stroke patients are admitted to the Acute Medical Care

Unit (AMCU). The data was collected retrospectively from case sheets and medical records. Cases of stroke are identified from specific codes recorded at the time of admission. Patient information such as age, gender, village, mandal, district, diagnosis, family history, habits, date of admission, date of discharge, and vital status were noted in the data sheets from available medical records. The data from all the data sheets were entered into the database MS Office Excel sheet. The collected information and data were compiled and analyzed using appropriate statistical methods.

2.2 Statistical Analysis

The collected information and data were compiled and analyzed using appropriate statistical methods. Percentage was calculated for the subjects with respect to their demographic variables. Association between age and smoking and alcohol intake in context of stroke prevalence was assessed by chi-square test with 1 degree of freedom (df) and two-tailed *P*-values.

3 Results

3.1 Demographic Characteristics of Stroke Patients

The data on demographic and clinical characteristics of the study population are depicted in Table 1. The study comprises of 4068 stroke cases, with the majority of stroke incidences being reported in males (64.2%) than in females (35.8%). In the present study, only 2.7% of strokes incidents occurred in individuals <40 years old, 4.9% in 41–50 years old, 18.2% in 51–60 years old, and 74.2% in ≥60 years old (Table 1). The number of stroke cases reported during the year 2014 were 2365 and during the year 2015 were 1703. The mean age of study population was found to be 58.9 ± 18. We observed that most of the stroke patients (59.4%) had BMI >25 kg/m^2. We also observed that ischemic stroke was the most frequent type of stroke (57.9%) followed by intracerebral hemorrhage (29.2%), subarachnoid hemorrhage (7.3%), transient ischemic attack (0.9%), and other types of stroke (4.7%). Table 1 also shows the frequency of identified predecessors and habit-related risk factors. History of hypertension was the most common antecedent risk factor in a total of 2298 (56.2%) patients. Similarly, history of diabetes was identified in a total of 1315 (32.3%) patients. In case of habit-related risk factors like smoking and alcohol, our results revealed that 53.1% and 47.1% of stroke patients had smoking and drinking habits, respectively.

See Table 1: Demographic details of stroke patients in our study.

Table 1 Demographic details of stroke patients in our study

Characteristics	Patients	Percentage (%)
Age		
≤40	109	2.7
41–50	201	4.9
51–60	741	18.2
61–70	1882	46.3
≥70	1135	27.9
Gender		
Male	2610	64.2
Female	1458	35.8
Year		
2014	2365	58.1
2015	1703	41.9
Body mass index (BMI)		
<25	1651	40.6
≥25	2417	59.4
Risk factors		
Hypertension	2298	56.2
Diabetes	1315	32.3
Smoking	2157	53.1
Alcohol	1912	47.1
Other	921	23.6
Type of stroke		
Ischemic	2355	57.9
Subarachnoid hemorrhage (SAH)	295	7.3
Intracerebral hemorrhage	1185	29.2
Transient ischemic attack (TIA)	35	0.9
Other	198	4.7

3.2 Distribution of Stroke Cases on the Basis of Age and Smoking/Alcoholic Status

Distribution of stroke cases on the basis of age and smoking/alcoholic status is summarized in Table 2. Regarding smoking and alcoholic status of study subjects in the present study, it was observed that out of 2157 smokers, 843 (39.1%) were below 60 years of age, whereas in case of nonsmokers, only 10.9% patients were below 60 years old. Similarly, we also found variation among nonalcoholic and alcoholic stroke patients. A statistically significant association was found both for smoking ($\chi^2 = 419.1$ and $p < 0.001$) and alcohol ($\chi^2 = 68.7$ and $p < 0.001$) as risk factors in stroke causation.

See Table 2: Distribution of stroke cases on the basis of age and habit-related risk factors.

Table 2 Distribution of stroke cases on the basis of age and habit-related risk factors

Habits	Age group			Chi squared (p-value)
	≤60	≥60	Total	
Smoking				
Nonsmoking (%)	208 (10.9)	1703 (89.1)	1911 (100)	
Smoking (%)	843 (39.1)	1314 (60.9)	2157 (100)	
Total (%)	1051 (27.1)	3017 (72.9)	4068 (100)	419.006 ($p < 0.001$)
Alcohol intake				
Nonalcoholic (%)	441 (20.5)	1715 (79.5)	2156 (100)	
Alcoholic (%)	610 (31.9)	1302 (68.1)	1912 (100)	
Total (%)	1051 (27.1)	3017 (72.9)	4068 (100)	68.729 ($p < 0.001$)

Chi-squared with Yates' correction (df = 1), *P*-value (the two-tailed) less than 0.05 was considered significant

4 Discussion

In most of the developed countries, stroke becomes the leading cause of disability, dementia, and death. Moreover, stroke is an influencing factor for epilepsy and is a leading cause of functional impairments, with 20% of survivors needing institutional care after 3 months and 15–30% being permanently disabled (Steinwachs et al. 2000). According to the India stroke factsheet updated in 2012, the assessed age-adjusted prevalence rate for stroke ranges between 84 and 262/100,000 in rural and between 334 and 424/100,000 in urban areas (Taylor and Suresh 2012). Our present study showed a higher prevalence rate in urban areas of the Warangal district mostly because of sedentary lifestyle, unhealthy food habits, and excessive stress levels. The present study reported that frequency of stroke incidence is higher in males compared to females (64.2% vs. 35.8%), and similar type of results was also reported by a previous study (Dalal et al. 2008). This gender-wise variation may be due to smoking, alcohol consumption, and stress levels in adult males.

In the present study, the mean age of study population was found to be 58.9 ± 18. The average age of the stroke patients in developing countries is 15 years lesser compared to developed countries (Bonita et al. 2004). In India, approximately one-fifth of the stroke patients admitted to hospitals with first-instance strokes were about ≤40 years old (Durai Pandian et al. 2007). From our research, we established that only 2.7% of strokes incident occur in individuals less than ≤40 years old, 4.9% in 41–50 years old, 18.2% in 51–60 years old, and 74.2% in ≥60 years old. A similar pattern was observed in community-based studies from India and other developed countries (Feigin et al. 2003; Das et al. 2007). High occurrence of stroke risk factors may lead to early atherosclerosis (Poungvarin 1998).

The extensive geographical difference in the distribution of stroke around the globe may be due to exposure to different risk factors and variation in genetic susceptibility. In the present hospital-based study comprised of comparatively large sample size of 4068 stroke cases and categorized into ischemic, subarachnoid

hemorrhage (SAH), intracerebral hemorrhage (Moghaddam, #1), and transient ischemic attack (TIA), the results show that risk of stroke increases with age. We also found that most of the stroke patients (59.4%) had BMI >25 kg/m^2. Meta-analysis carried out by Strazzullo P. et al. revealed that relative risk for ischemic stroke for overweight and obese subjects were 1.22 and 1.64, respectively, while relative risk for hemorrhagic stroke for overweight and obese people were 1.01 and 1.24, respectively (Strazzullo et al. 2010). In another meta-analysis study, Hiroshi Y et al. found that BMI >25 kg/m^2 had a substantial association with the incidence of stroke cases (Yatsuya et al. 2010).

According to Feigin et al., the frequency of IS, SAH, and ICH ranges from 67.3% to 80.5%, 6.5% to 19.6%, and 0.8% to 7.0%, respectively (Feigin et al. 2003). In our study, the frequency of ischemic (IS), subarachnoid hemorrhage (SAH) and intracerebral hemorrhage (Moghaddam, #1) in Warangal, Telangana region, was 57.9%, 7.3%, and 29.2%, respectively, which are more or less within the ranges reported by Feigin et al. Of the 2157 smokers in the present study, 843 (39.1%) were below 60 years of age; whereas in case of nonsmokers, only 10.9% of patients were below 60 years old. We found a statistically significant variation between age of stroke patients and smoking ($p < 0.001$). Our results also show that alcohol intake promotes stoke in younger people significantly ($p < 0.001$). Therefore, it is indicated that smoking and alcohol consumption play a significant role in the occurrence of stroke in younger people. Previous studies also reported that smoking and alcohol intake were associated with ischemic stroke (Mukamal et al. 2005; Xu et al. 2013). Another study also reported that smoking and alcohol intake were significant risk factors for intracerebral hemorrhagic stroke (O'Donnell et al. 2010).

5 Conclusions

Stroke is a major problem in our society leading to physical disability which is affecting the life of the patients as well as their family members. Therefore, there is a need to provide structured clinical management in treating emergency stroke cases. Stroke care services with organized multidisciplinary teams are required in Telangana region. The condition of the patients transmitted to MGM Hospital from other districts worsens due to the delay in acute treatment. Hence, stroke unit implementation is needed in every district of Telangana region. Lack of awareness and knowledge about stroke in the general public and people in rural areas is causing delay in the acute medical treatment leading to permanent physical impairment. The necessity of educating people and health-care professionals about the implementation of effective stroke preventive strategies cannot be overemphasized. The fact that nearly two-thirds of stroke survivors were significantly disabled 1 month after the stroke incidence demands better care during acute stage to minimize disability as well as long-term strategies to rehabilitate the disabled. For public awareness, the risk factors associated with stroke need to be frequently broadcasted both in print and electronic media. The important component of such public awareness program

would be to promote healthy diet, regular exercise, avoidance of smoking and alcohol, and effective management of obesity, diabetes mellitus, and hypertension.

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Compliance of Patients with Acute Coronary Syndrome with Treatment Following Their Hospitalization from the Cardiac Coronary Unit

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1 Introduction

The patient's noncompliance is not a modern phenomenon as it has been the subject of many studies that have taken place over the last 50 years (Choudhry and Winkelmayer 2008). The compliance rate is recorded at 50% 2 years after starting treatment. Particularly in chronic conditions, where medication becomes necessary over the course of a long time, patient's compliance has been reported at 43–78% (Keller et al. 2011).

Acute coronary syndrome (ACS) is one of the most common causes of morbidity and mortality worldwide (Trost and Lange 2011). Although secondary prevention is considered to be necessary, research evidence suggests that patients are noncompliant with their medication (Thakkar and Chow 2014).

The compliance rates after ACS are between 40% and 75%, with adverse effects such as morbidity, mortality, and increased health costs (Desai and Choudhry 2013; Ho et al. 2009). Poor compliance of cardiac patients is associated with increased

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readmissions ranging from 10% to 40%, coronary interventions from 10% to 30%, and mortality from 50% to 80% (Thakkar and Chow 2014).

The compliance of patients with chronic diseases such as hypertension, cholesterol, diabetes, and obesity, which are predisposing factors for cardiovascular disease, reaches levels below 41% after the first year of onset of treatment. This makes compliance with treatment a serious social problem with significant consequences for public health (Srivatsan et al. 2014; Desai and Choudhry 2013).

2 Materials and Methods

2.1 Aim

The aim of the study was to measure the levels of compliance with the treatment of patients who suffered from acute coronary syndrome. Also, we tried to investigate the factors contributing to the noncompliance and relate the noncompliance rates with the characteristics of the sample, the nature of the disease, the socioeconomic factors, and the health system.

2.2 Study Design

This was a retrospective quantitative study. The data were collected from the e-medical records of the hospital. The survey was conducted from December 2017 to February 2018, and the sample consisted of 100 patients who were hospitalized in the coronary care unit of the general hospital of Pyrgos Ileias, Greece. The sample was a sample of convenience, and the answers to the questionnaires were given after patients were informed for the purposes of the study and gave written consent.

Patients who were included in the study have agreed to answer the questionnaires and participate to the study, had been hospitalized at least 12 months before the beginning of the study, and spoke Greek or English. Exclusion criteria included hospitalization less than 12 months before the start date, patients with mental disorders, and the lack of understanding of one of the two languages mentioned above.

2.3 Tools

Demographic data and pretreatment risk factors of ACS were collected. The GR-SMAQ and ARMS scales were used. The Simplified Medication Adherence Questionnaire (GR-SMAQ) is a self-completed questionnaire used by P. Theofilos in 2012 to determine compliance in 10 patients with lung cancer (Alikari et al. 2017). Initially, it was used to measure the compliance of patients receiving antiretroviral

therapy (Knobel et al. 2002), and it has also been used for compliance with renal medicine (Arenas et al. 2010). It consists of six questions. The level of compliance is determined by the total score the respondents achieve. There are three grades of compliance: low (total score ≥ 3), moderate (total score 1 or 2), and high (total score 0) (Alikari et al. 2017). Tabacnick and Fidell (2007) in their study of the reliability and validity of the questionnaire reported that 10 patients should be assigned to each question to be sufficient. So the sample of 100 patients in the study is considered adequate.

The Adherence to Refills and Medications (ARMS) scale was introduced in 2004 following an interdisciplinary team effort to create a compliance measurement scale, which would be easy to complete even among those with low education level. The ARMS scale is based on the Morisky and Hill-Bone Compliance to High Blood Pressure Therapy scales. It consists of 12 Likert-type questions. Responders have to choose one of four answers "never," "rare," "sometimes," and "always" which receive values from 1 to 4. Lower score corresponds to higher compliance. There are three grades of compliance: low (total score > 34), moderate (total score 13–34), and high (total score ≤ 12). This scale has been used to determine compliance in patients with chronic diseases. The usability is its main advantage. Kripalani et al. (2009) measured compliance in patients with coronary artery disease, while Mayberry et al. used it in research on diabetes (Mayberry et al. 2015).

2.4 Ethics

In order to carry out the study, the 41/30-1-18 permission was taken from the Scientific Council of the Hospital. There was anonymity of the participants. The patient's participation was voluntary, and there was no funding.

2.5 Statistical Analyses

For the description of the continuous variables, we used the mean value and the standard deviation, while for the discrete variables, the frequency (%). In order to investigate the correlations between the variables, t-test, and control, X2 was used and the value of statistical significance was set to 0.05. The statistical analysis was carried out using IBM SPSS 21.0 statistical package.

3 Results

The majority of the people who were hospitalized in the CCU were male (76%), married (71%), retired (49%), had no high school level education (64%), had health insurance (91%), and aged 62.7 ± 13.2 years. Three months after hospitalization,

the readmission rate was 15%, while 6 and 12 months after, it was 21% and 23%, respectively. The demographic characteristics of the participants are shown in Table 1.

At the time of admission to CCU, 76% of the sample had abnormal values for systolic arterial pressure, 24% for diastolic blood pressure, 88% for cholesterol, and 27% for diabetes mellitus. Also, 82% of the patients smoked and 39% of them exercised. Three months after their hospitalization to CCU, 30% of patients had abnormal levels of systolic blood pressure, 42% had abnormal levels of cholesterol, and 21% had abnormal levels of diabetes mellitus. Moreover, 15% remained smokers, while 55% exercised. Six months after hospitalization, 27% of patients had abnormal levels of systolic blood pressure, 15% of cholesterol, and 27% of diabetes mellitus, while 9% still smoked and 58% were exercised. After 1 year of discharge from the CCU, 32% of the patients had abnormal levels of systolic blood pressure and cholesterol, and 50% of the patients had abnormal levels of diabetes mellitus, while 27% continued smoking and 59% exercised (see Table 2).

Table 1 Patient demographics

	Variables	*N* (%)
Gender	Males	76 (76%)
	Females	24 (24%)
Marital status	Unmarried	11 (11%)
	Married	71 (71%)
	Widows	11 (11%)
	Divorced	7 (7%)
Profession	State employee	6 (6%)
	Private employee	6 (6%)
	Freelance	11 (11%)
	Retired	49 (49%)
	Farmer	11 (11%)
	Unemployed	17 (17%)
Education level	No high school	64 (64%)
	High school	28 (28%)
	University	8 (8%)
Insurance		91 (91%)

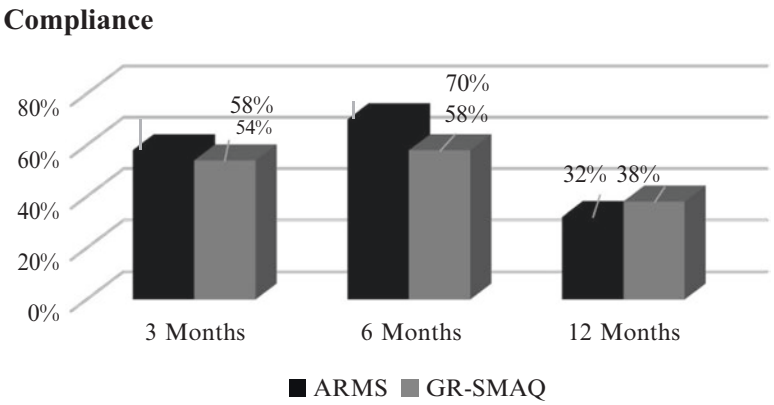
Table 2 Rate of patients who had abnormal levels of systolic blood pressure, diastolic blood pressure, cholesterol, blood glucose, smoking, and exercise at admission and 3, 6, and 12 months after hospitalization

Variable	Admission	3 months	6 months	12 months
Systolic blood pressure	76	30	27	32
Diastolic blood pressure	24	9	6	3
Cholesterol	88	42	15	32
Blood glucose	27	21	27	50
Smoking	82	15	9	27
Exercise	39	55	58	59

The compliance of patients with their treatment 3 months after hospitalization to CCU was 58% as it was measured with ARMS scale and 54% with the GR-SMAQ scale. Six months after hospitalization, the compliance rates were 70% and 58%, respectively, and after 1 year, the rates were 32% and 38%, respectively (Graph 1).

By correlating the compliance of the patients as it was measured with ARMS and GR-SMAQ with the normal value of systolic blood pressure, diastolic blood pressure, smoking, exercise, cholesterol, readmission, and diabetes mellitus 3, 6, and 12 months after hospitalization to CCU, we found that noncompliance was a statistically significant difference compared to compliance as regard to systolic blood pressure 1 year after hospitalization (Table 3). For the remaining variables, no statistically significant difference was detected. The only case that the p value was close to 0.05 was for the readmission rates 3 months after hospitalization ($p = 0.075$). Compliance and noncompliance were also correlated with gender, age, level of study, and family and occupational status on both scales, and no statistically significant difference was observed ($p > 0.05$).

A prediction model for both scales was developed using logistic regression method. According to the results for the ARMS scale, patients who readmitted to CCU had 68.9% less chance of showing compliance, and patients who had normal levels of systolic blood pressure were 3.5 times more likely to be adherent to their treatment. Similarly, according to the GR-SMAQ scale, the respective values for readmission and systolic blood pressure were 61% and 2.8 (Table 4).



Graph 1 Compliance of patients with treatment 3, 6, and 12 months after hospitalization to CCU

Table 3 Variables that showed statistically significant difference

Scale	Compliance (%)	No compliance (%)	*P*
	Systolic arterial pressure		
ARMS	12 (92.3%)	1 (7.7%)	0.045
GR-SMAQ	10 (90.9%)	1 (9.1%)	0.045

Table 4 Logistic regression

Scale	Variable	*B*	*P*	Exp(*B*)	95% CI for EXP(*B*)
ARMS	Readmission	−1.167	0.048	0.311	0.098–0.988
	Normal systolic arterial pressure	1.263	0.013	3.537	1.308–9.563
GR-SMAQ	Readmission	−0.941	0.088	0.390	0.133–1.149
	Normal systolic arterial pressure	1.027	0.031	2.793	1.099–7.098

4 Discussion

This study investigated the compliance with the treatment of 100 patients who were hospitalized in CCU after ACS. The readmission rate was found to increase gradually over time, from 15% at 3 months to 23% at 12 months after discharge from CCU.

We found that the percentage of pathological values of systolic arterial pressure was 76%. Similarly, the rates for hyperlipidemia and diabetes mellitus were 88% and 27%, respectively. Increased percentages in these predisposing factors are also reported in the literature where the percentage of patients with hypertension, dyslipidemia, and diabetes mellitus was 72.6%, 55.9%, and 55%, respectively (Ahmad et al. 2011).

The percentage of people who continued to smoke 12 months after the ACS was 27% and is almost the same as reported by Ahmad et al. (2011). However, it appears to be significantly reduced from its initial value of 82%. It was also lower at 3- and 6-month intervals, which is also in agreement with the findings of a study by El-Toukhy et al. (2017). Also, in relation to physical exercise, the percentage of people who exercised increased, which is also shown in the literature (El-Toukhy et al. 2017).

The measurement of compliance was performed at three-time intervals and with two scales, which enhances the validity of the results (Mathews et al. 2015). Three months after admission, the compliance rate was 58% with the ARMS scale and 54% with GR-SMAQ scale. The percentages were quite low and agree with the literature (Faridi et al. 2016). Six months after admission, the compliance rate was 70% with the ARMS scale and 58% with GR-SMAQ scale. The first rate agrees with what was measured in a study of 7425 subjects (Mathews et al. 2015) and the second with the study of Molloy et al. (2014). Twelve months after discharge from CCU, compliance is at even lower levels. The compliance with ARMS scale was found at 32% and with the GR-SMAQ scale 38%. Approximately at the same level were the rates recorded by other studies in literature (Nguyen et al. 2017; Molloy et al. 2014; Puchin'yan et al. 2011).

In our study, it was found that compliance is increasing after 3 months, at six it is at the highest level, and then it decreases again and reaches the lowest level at 12 months. Similar pattern was also recorded by Molloy et al. (2014).

According to the answers given by the responders on the GR-SMAQ scale, most of them stated that they forget to take their medication and that they did not receive them at the right time. According to answers from ARMS scale at 3 and 6 months after hospitalization, responders forget to take their medication, decide for themselves not to take it, find it difficult to remember because they are taking a lot of

medicines, and they cannot afford them. Similarly, at 12 months, patients stated that they forget to visit a GP for prescriptions and their medications are depleted. The fact that they forget their medication seems to be a major cause of noncompliance and is also reflected in other studies in the literature (Cheng et al. 2015; Mathews et al. 2015). It should also be noted that all patients showed high compliance in the time interval before the visit to the doctor. The phenomenon of increasing compliance for time intervals before and after a visit to a doctor is often observed and is known as compliance with "white coat" (Gehi et al. 2007).

Also, we found statistically significant relationship between compliance and systolic arterial pressure according to the ARMS scale 6 and 12 months after hospitalization and to the GR-SMAQ scale 12 months after hospitalization. The same effect was found in a study by Kripalani et al. (2009) on compliance in coronary patients using the ARMS scale. It has also been found that people who comply do not relapse in order to avoid readmission. This agrees with Puchin'yan et al. (2011) who stated that readmission to hospital is a significant burden on the individual and the family, with social and economic implications.

We did not find any correlation between compliance and noncompliance in relation to gender, age, marital status, occupational status, and education level in both scales. This result agrees with Gehi et al. (2007) who found that compliance is independent of age and educational level. Also, Nguyen et al. (2017) found no correlation of gender with compliance. Jimmy and Jose (2011) states that compliance is independent of demographic factors, and Puchinyan et al. correlated compliance with endogenous factors (Puchin'yan et al. 2011).

Finally, with the logistic regression model, it was found that patients who were readmitted to CCU had 68.9% less chance of showing compliance, and patients with normal systolic arterial pressure were 3.5 times more likely to be adherent to treatment. In agreement with our results, Puchinyan et al. and Mathews et al. found that patients who did not comply to treatment had increased probability of readmission (Mathews et al. 2015; Puchin'yan et al. 2011).

5 Limitations

The results of the study are based on self-reporting, so there is a risk that the answers will be false, either in line with social desire or to avoid disapproval. Also, the sample includes a population from a single hospital in a county, so the results cannot be generalized to the entire population.

6 Conclusions

Compliance with the medication of patients who suffered from ACS is quite low mainly due to endogenous and economic factors. Those who comply usually have normal systolic arterial pressure and are not readmitted in the hospital.

The results of noncompliance are significantly associated with socioeconomic implications. Doctors and nurses play an important role in increasing compliance since interactions with patients can identify the causes of noncompliance and adopt appropriate techniques.

The use of wearable devices is an advanced solution to this problem. With the usage of this kind of technology, health-care providers can monitor the vital signs and the habits of patients with ACS and can phone them or send them e-mail or text messages in order to remind them their "obligations" and increase their compliance with the treatment. Another solution to this problem of low compliance is the creation of advisory groups, the online training, and the regular checking of the adherence level.

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Using a Virtual Reality Serious Game to Assess the Performance of Older Adults with Frailty

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1 Introduction

Frailty is a common clinical geriatric syndrome. It is related to an elevated risk for adverse health outcomes, and its importance is rising along with the increased life expectancy of the global population. Current research focuses in the early detection of frailty in order to allow affected older adults to benefit from relevant interventions, remain independent for longer, and thus have a better quality of life (Kojima et al. 2016).

There is a plethora of tools for the assessment of cognition, including standardized neuropsychological assessment tests and screening batteries (Scott and Donnelly 2005). Moreover, these tools are continually adapted from the typical paper-and-pencil format to a computerized format (Chan et al. 2018), allowing for administration through personal computers (PCs) and tablet devices. This shift to computerized tools

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aims to capitalize on the advantages of modern ICT technologies such as accurate measurement of performance, automatic administration or self-administration, remote monitoring, and automatic reporting (Zygouris and Tsolaki 2015).

While there has been considerable progress in the creation and adaptation of computerized cognitive screening tools, there is a distinct lack of computerized tools for frailty screening. Despite the plethora of available screening tools for frailty, most of them are available only in the traditional paper-and-pencil format and require a lot of time and expertise to administer (IHUB 2017). There is a need for the creation of computerized frailty screening tests, which can be self-administered for remote users, and this study is a first step in that direction.

1.1 Virtual Reality Serious Games as Screening and Training Instruments

Gold standard diagnostic tools can differentiate people with cognitive decline and frailty from healthy populations, but they cannot provide meaningful information about the behavioral patterns they follow and the expected differences from normal perceived behaviors as they do not refer to everyday activities (Morganti 2004). Recently, behavioral patterns have been studied as risk factors for a number of health conditions and mortality, including frailty (del Pozo-Cruz et al. 2017). Other similar studies try to determine social and behavioral factors associated with frailty trajectories (Chamberlain et al. 2016). As the traditional screening instruments target specific cognitive domains, the tasks implemented in diagnostic processes are highly repetitive and monotonic; in contrast, everyday functioning is dynamic, complex, and multitasking.

Apart from the use of computerized assessment tools in cognitive screening, there is an increasing number of older people with (or without) cognitive decline who use computerized cognitive training applications in order to maintain and improve their cognitive health. This dual purpose (screening and intervention) is served mainly by memory tasks, but there are other VR applications which offer enjoyable means of exercising multiple cognitive abilities, like visuospatial skills, attention, and executive function (Segkouli et al. 2014). VR technology can offer stimulating environments with high ecological validity and thus allow for the monitoring of more spontaneous human behavior monitoring (Parsons 2015).

In this context, VR technology has the potential to assess cognitive functions while being enjoyable for end users if it is used to present tasks resembling everyday activities. Such an application is the ECO-VR (Oliveira et al. 2016), a 3D VR environment of a house used to stimulate multiple cognitive functions such as prospective memory, spatial orientation, concentration, problem-solving, initiative, and inhibition. It is remarkable that there are a lot of "Virtual Supermarket applications" created by various research teams and for various purposes. Waterlander et al. (2011) created a 3D environment to study consumer food purchasing behavior. van Herpen et al. (2016)

used a simulated grocery store to examine consumer behavior for specific product categories and Cromby et al. (1996) for people with learning disabilities. It is argued that shopping in a supermarket is a very common cross-cultural activity that necessitates the simultaneous activation of different cognitive functions. Thus, it translates to an ideal VR task for stimulating and assessing cognitive functions of healthy older adults or older adults with mild cognitive problems (Zygouris et al. 2016).

1.2 Study Objectives

In this study, an experimental screening process has been designed as a quasi-experiment in order to test whether a Virtual Reality Serious Game (VRSG) like the Virtual Supermarket can detect frailty over healthy populations and to find which specific domains of the perceived behavior are more affected.

Answering these research questions is important for both the research on frailty as well as the clinical praxis because (1) it comes more natural to observe different behavioral patterns in complex everyday activities like shopping, (2) it appears to be more enjoyable for users to take self-administrated screening challenges in a computer game, and (3) if early detection of frailty turns out to be possible by these means, it is important for intervention planning. Moreover, complex activities like shopping require the employment of various skills and cognitive abilities simultaneously and better reflect the need to assess real-life limitations of the Instrumental Activities of Daily Living (IADL) (Lawton and Brody 1969) rather than isolated performance standardized testing in controlled environments. The study was performed in the context of the FrailSafe European research project, dealing with the investigation of frailty through manual and automatic data acquisition regarding clinical, physiological, cognitive, and behavioral aspects.

2 Materials and Methods

This study used the latest version of the Virtual Supermarket application (Zygouris et al. 2015) and involved elder volunteers from day care centers located in France, Greece, and Cyprus. The following sections will describe the characteristics of the participants and will explain the tested application and the experimental protocol.

2.1 The Virtual Supermarket and Way of Use

The virtual 3D environment was projected through a desktop VR application (low immersion, no use of special hardware) on a tablet computer. The VSM mimics an everyday shopping experience while it monitors user's behavior by

measuring key-characteristic parameters like the kind and quantity of products purchased. In this gamelike environment, users are asked to do their shopping based on a predefined shopping list which contains a number of randomly selected items. After each game session, the player's performance is reported back to a server for further statistical analysis. Some screenshots of the application can be seen in Figs. 1 and 2, while the game tasks are described in more detail in the following section.

Fig. 1 Screenshot from the Virtual Super Market application (overview of the virtual environment)

Fig. 2 Screenshot from the payment screen (cashier desk view)

2.2 Description of the Game Tasks

A list of random products is presented to the players at the beginning of the task. This list remains visible throughout the task. The player is then asked to navigate the virtual environment of the supermarket in order to find the listed products in the shelves, purchase the correct quantity of each product, and then pay at the cashier's desk.

The navigation in the virtual 3D space is possible with the help of visual marks appearing as green footprints on the floor. By touching one of those, the player's position is updated by a smooth movement. The left-right scrolling is used by players to rotate a virtual camera around the 3D space (head camera at the height of the eyes). Touching a product adds this product to the shopping cart.

After purchasing all the products in the list, which appear on the screen throughout the duration of the game (the goal was to purchase four to eight items), the players were asked to proceed with the checkout. In the last navigation task, players are asked to locate the cashier's desk and move there before paying in Euro bills and coins as seen in Fig. 2. It should be noted that the player has to enter the exact amount displayed in the till (no change).

The last screen in the game is the confirmation that the payment has been completed and a report on the user's activity is displayed. This includes the products purchased, their quantities, and the total time needed for completion.

The VSM is offered in three Levels of Difficulty (LoD) to let users adopt the perceived difficulty to their abilities and preferences:

Level 1: In this introductory level, users have to find and purchase 4 products, 1 item from each product category (e.g., 1 tomato, 1 tin of beans, 1 yoghurt, and 1 spaghetti).

Level 2: More than one product from each product category appears in the shopping list (e.g., 4 tomatoes, 3 tin of beans, 1 yoghurt, and 2 packs of spaghetti).

Level 3: The same as in Level 2, but the shopping list is hidden during gameplay (not used).

2.3 Description of Participants and Demographics

The study received institutional review board (IRB) approval from each participating institution, and all study participants gave their informed consent prior to their inclusion. As the study included cognitively healthy individuals, each participant had the ability to provide informed consent. Recruitment criteria for the people with frailty included typical symptoms of frailty, but not dementia. Participants had to be 70 years old and over, able to use a tablet computer, and willing to participate in this study. From people with proven ability to perform the task independently, those

diagnosed with depression or high levels of stress were excluded. In addition, any other disorder that may have caused cognitive impairment, such as psychiatric disorders, was an exclusion criterion.

In total, the body of participants consisted of eighty ($N = 80$) older adults, with an average age of 78.08 years (SD = 5.479). From those, 39 were found to be non-frail and thus comprised the control group (CG), 30 people were found in a pre-frail state (PF), and the other 11 presented a frail phenotype (FR). The sizes of the study groups and other demographic information of the participants are presented in Table 1. Although education was not considered a parameter which could possibly affect the aforementioned groups, a confirmatory test on years of education and frailty status was made by using the one-way ANOVA [$F(2.77) = 1.615$, $p = 0.205$].

The participants were assigned to one of the three groups according to their level of frailty as assessed by Fried's criteria (Fried et al. 2001), namely, shrinking (weight loss and sarcopenia), weakness, poor endurance, exhaustion, slowness, and walking time. Subjects were characterized as non-frail in the absence of any criterion, as pre-frail ("intermediate" as by Fried) in the presence of 1–2 criteria, and as frail in the presence of 3 or more criteria.

Apart from a categorization according to the frailty status (phenotype), participants went through a Comprehensive Geriatric Assessment (GCA) which included cognitive and functional assessment. Functional assessment was conducted through the following scales: the Activities of Daily Living (ADL) (Wallace and Shelkey 2007), the Instrumental Activities of Daily Living (IADL), and the short screening version of the Mini Nutritional Assessment (MNA-SF) (Kaiser et al. 2009).

Cognitive functioning was evaluated using the standard screening tools Montreal Cognitive Assessment Scale (MoCA) (Nasreddine et al. 2005) and the Mini-Mental State Examination Scale (MMSE) (Nasreddine et al. 2005). It should be noted that a MMSE score below 24 (MMSE <24) was an exclusion criterion. The 15-item version of the Geriatric Depression Scale (GDS) was used for depression screening.

Table 1 Demographics of participants

Parameters	Groups of participants			All cases
	Control group (CG)	People with pre-frailty (PF)	People with frailty (FR)	
N	39	30	11	80
Sex (males/females)	10/29	6/22	3/8	19/61
Age (in years)	77.05	78.00	81.91	78.08
	(SD = 4.931)	(SD = 5.626)	(SD = 5.718)	(SD = 5.479)
Education (in years)	15.13	13.43	13.27	14.24
	(SD = 4.824)	(SD = 3.645)	(SD = 4.174)	(SD = 4.364)

2.4 Performance Metrics

The scoring parameters used to describe the performance of the players include the degree the game objectives were completed and the errors made during the game:

Errors related to the product types (itemTypesError): This is the error rate of the player regarding the types of products purchased, and its numerical expression is ABS (itemTypesBought – itemTypesListed)/itemTypesListed.

Errors related to the number of products (item quantities error): This is the error rate of the player regarding the number of products purchased. It is calculated as ABS (item quantities bought – item quantities listed)/item quantities listed.

Payment errors (money error): This is the error rate of the player regarding the payment process (bill selection and total amount paid). It is calculated as ABS (money paid – items bought value)/MAX (money paid, items bought value).

Based on the above, the VSM game performance metrics are defined as follows:

Duration (overall duration): This is the overall time measured in seconds. The player needed to complete the game tasks, including search, find, purchase the products in the list, and pay in the cashier's desk.

Selected item types (item types score): This is a score to measure the correctness in the types of products the user bought, compared to the types of products in the given list. It is calculated as 100 ∗ (1 – item types error).

Selected number of items (item quantities score): This is a sub-score used to measure the number of the items selected by the player compared to the total number of items in the given list. It is calculated as 100 ∗ (1 – item quantities error).

Payment score (money score): Additional metric used to measure how well the payment was performed after the game activity. It is calculated as 100 ∗ (1 – money error).

Score (overall score): This is a numeric descriptor of the player's performance during a single game session (excluding payment). It is calculated by combining the two scores item types score and item quantities score, weighted by 50% each. It is calculated as (item types score + item quantities score)/2.

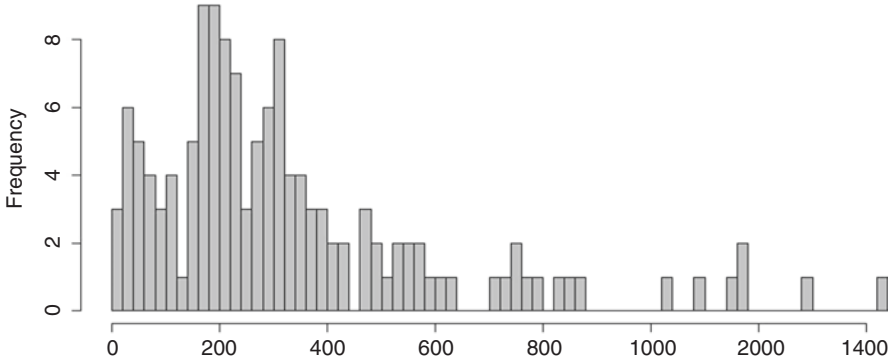

Fig. 3 Histogram of the game durations (in seconds)

2.5 Study Protocol and Experimental Conditions

A group of older adults participated in this study in a volunteer basis after they had received a short demonstration of the game (~ 10 minutes), signed a consent form, and shared their demographic information. All volunteers used the VSM application from the second semester of 2016 up to the autumn of 2017 under the same conditions.

Participants were recruited from local day care organizations, and they received the Virtual Supermarket game in a self-administration context on average 2.5 months after they were assessed with the neuropsychological test battery. The gaming sessions were self-administered in the participants' home environments. A regular training period of 2 days on average was esteemed during which the participants played the game 8 times on average, although there were also participants who had already played the game at previous times (e.g., some months before). Thus, only the last game sessions of each participant were taken into account for this study.

It is noteworthy that only the first two levels of difficulty were used in this experiment (visible shopping list). During preprocessing, game log recordings longer than 1500 seconds and shorter than 10 seconds were excluded from the analysis of the game duration (Fig. 3).

3 Results

Statistical analysis was performed using SPSS software (IBM), ver. 19. Unlike the years of education, age and scoring variables were found not normally distributed among the groups of participants according to the Shapiro-Wilk test of normality, and thus nonparametric tests were used to test the hypotheses of this study.

3.1 Game Results

The scores of the users (players) who participated in this study are presented numerically in Table 2 and graphically in Fig. 4. Series of rank-based nonparametric tests (Kruskal-Wallis H test) were performed on the data collected through the log files of the players. As seen in Table 2, statistically significant differences were found in both the game performance metrics, namely, the item types score ($p = 0.05$) and item quantities score ($p = 0.006$), as well as in the overall score ($p = 0.007$). In contrast, no statistically significant differences were found between user groups regarding the money score ($p = 0.268$) and the game duration ($p = 0.905$).

In a short gender analysis study using the Mann-Whitney U test, no statistically significant differences were found in performance metrics, namely, the overall score ($U = 569$, $p = 0.885$), item types score ($U = 546.5$, $p = 0.634$), item quantities score ($U = 562.5$, $p = 0.812$), and money score ($U = 75$, $p = 0.722$).

3.2 Association Test Results

In this section, results of correlation tests with neuropsychological test results and game performance metrics are presented. Bivariate correlations tests were performed with the Pearson correlation coefficient calculation (Table 3). Game duration, money score, IADL, and ADL gave no statistically significant results, and thus they were excluded from Table 3. Moreover, Overall Score was also omitted.

Table 2 The Virtual Supermarket game results

Parameters	Groups of participants			All cases	Chi-square test results
	Control group (CG)	People with pre-frailty (PF)	People with frailty (FR)		
Game duration (in sec)	298.934	349.472	327.637	321.176	X^2 (2) = 0.199
	(SD = 210.568)	(SD = 284.195)	(SD = 320.036)	(SD = 253.770)	($p = 0.905$)
Item types score (%)	87.820	75.833	59.090	79.375	X^2 (2) = 6.004
	(SD = 29.172)	(SD = 41.253)	(SD = 47.792)	(37.689)	($p = 0.050$)
Item quantities score (%)	87.428	76.746	52.050	78.558	X^2 (2) = 10.354
	(SD = 29.082)	(SD = 41.905)	(SD = 45.878)	(SD = 38.155)	($p = 0.006$)
Money score (%)	86.349	88.888	50.00	81.972	X^2 (2) = 2.637
	(SD = 35.079)	(SD = 33.333)	(SD = 57.735)	(SD = 38.931)	($p = 0.268$)
Overall score (%)	87.624	76.289	55.57	78.966	X^2 (2) = 9.929
	(SD = 29.092)	(SD = 41.499)	(SD = 46.228)	(SD = 37.759)	($p = 0.007$)

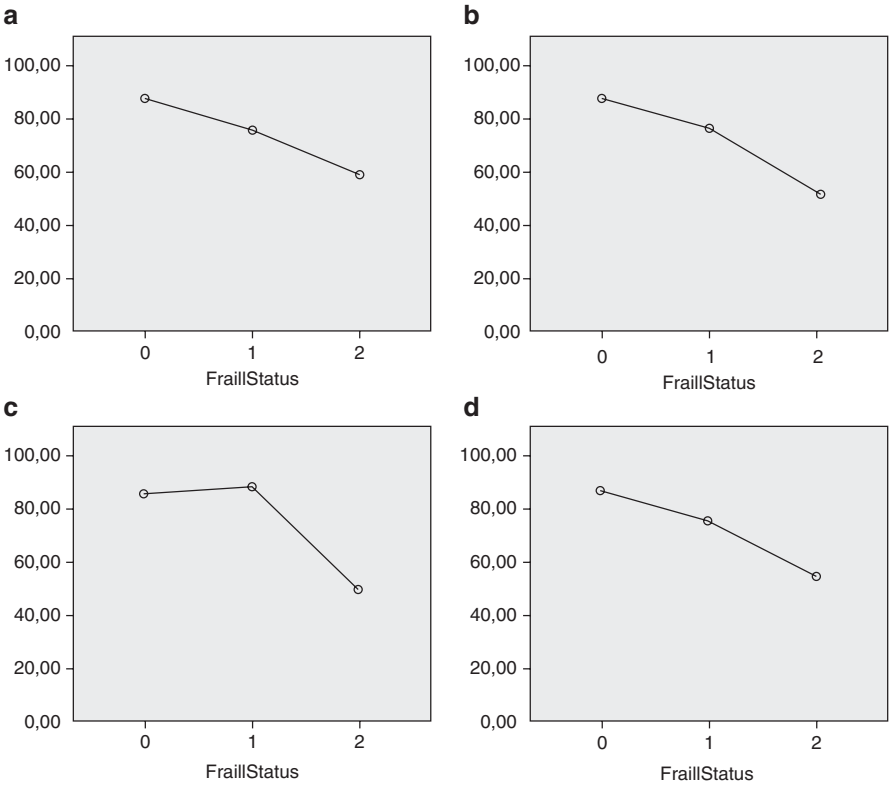

Fig. 4 Performance metrics of the three groups of participants in the Virtual Supermarket game which showed statistically significant differences (FrailStatus = 0 for healthy controls, 1 for PF, and 2 for FR). (**a**) Mean values of the items types score. (**b**) Mean values of the items quantities score. (**c**) Mean values of the money score. (**d**) Mean values of the overall score

A strong positive correlation was found between the two main performance metrics of the game, the item types score and the item quantities score, leading to the conclusion that people who made mistakes in the types of the products also made mistakes in the quantity of products purchased.

This indicates that the VSM and the overall user assessment protocol have the required internal validity as a testing environment. Similarly, a positive correlation was found between the two game performance metrics with nutrition (MNA) and a negative one with Depression (GDS). From the neuropsychological tests included in this analysis, MNA results were found to be correlated with GDS. From those results, depression seems to have an effect on nutrition, and both have a negative effect on game performance. Moreover, MOCA results were strongly correlated with MMSE results. Such a relationship was expected based on the fact that both of these screening tools measure global cognition.

Table 3 Pearson correlation test results between game performance metrics and neuropsychological test results

	Item types	Item quantities				
	Score	Score	MNA	MOCA	GDS	MMSE
Item types score	1	0.983**	0.361**	−0.037	−0.258*	−0.026
		($p < 0.001$)	($p = 0.001$)	($p = 0.743$)	($p = 0.021$)	($p = 0.818$)
Item quantities score	0.983**	1	0.378**	−0.030	−0.276*	−0.018
	($p < 0.001$)		($p = 0.001$)	($p = 0.790$)	($p = 0.013$)	($p = 0.873$)
MNA	0.361**	0.378**	1	0.008	−0.471**	−0.064
	($p = 0.001$)	($p = 0.001$)		($p = 0.944$)	($p = 0.000$)	($p = 0.571$)
MOCA	−0.037	−0.030	0.008	1	−0.071	0.628**
	($p = 0.743$)	($p = 0.790$)	($p = 0.944$)		($p = 0.533$)	($p < 0.001$)
GDS	−0.258*	−0.276*	−0.471**	−0.071	1	−0.049
	($p = 0.021$)	($p = 0.013$)	($p = 0.000$)	($p = 0.533$)		($p = 0.667$)
MMSE	−0.026	−0.018	−0.064	0.628**	−0.049	1
	($p = 0.818$)	($p = 0.873$)	($p = 0.571$)	($p < 0.001$)	($p = 0.667$)	

*Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed)

In addition to the above, a multinomial logistic regression (MLR) analysis was performed, taking as inputs the two-performance metrics (item quantities score and item types score) in order to test if a frailty prediction model could have been generated from the data produced by the game. This model will try to predict the nominal dependent variable of frailty status given the two independent variables of game performance, the item types score and the item quantities score. It was found that the fitting information of this model is significant with X^2 (4) = 15.662, p = 0.004. Overall, it is more likely that an older adult is in a frail or pre-frail state if he/she has made some mistakes (errors) while playing the Virtual Supermarket game than if he/she had made no mistakes.

4 Discussion

By using Virtual Reality technology for screening purposes, it was found that the performance of users was associated with frailty in older people, and thus the VSM could effectively distinguish between frail and non-frail subjects. Apart from the confirmation of the VSM's screening ability, the more detailed results of this study could allow for the examination of particular parameters of the subject's behavior which are affected by frailty.

Lower scores in cognition and depression tests were found to be associated with the frailty phenotype, similar to the results seen in Fried et al. (2001). The objective of our study however was to test for differences between people with frailty, people

with pre-frailty, and healthy controls in spatial orientation, short-term memory, selective attention, and speed of processing.

Other applications have also used everyday activities to detect signs of frailty. The ECO-VR (Oliveira et al. 2016) used home-based tasks like moving objects from room to room, watching TV, and listening to voice messages. Similarly, the VSM examined the behavior of the subjects in a virtual shopping experience. Analysis of performance in the VSM exercise was based not only on the degree to which the game goals were achieved but also on the number of errors committed during gameplay.

Under the common convention followed in similar studies, a training period was necessary (Tarnanas et al. 2013) to let people get familiarized with the use of the VR and become comfortable with the simulated environment. Finally, our analysis showed that although memorization of the shopping list and the product locations in the 3D space was a difficult task for the people with frailty, other tasks such as payments were not equally affected. Moreover, the time players spend playing the VSM game could not be considered useful to sense cognition frailty signs, possibly because the differences in game duration were due to different searching/navigation strategies adopted by the participants, i.e., some preferred to search products one by one, while others tried to purchase all products at once (in a single pass).

To further access if time (game duration) is a useful metric in the screening process, in future research, we will add some additional performance metrics in the VSM game and will repeat the screening process. These additional metrics, like the virtual distance subjects covered in a single game session, the sum of the rotation degrees (virtual camera) and the number of unnecessary corridor passes will let us understand the root causes of time delays.

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Characteristics and Survival Rates in Ward Patients Requiring Evaluation by Intensivist in Greece

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1 Introduction

Patients at risk should be admitted to the ICU if there is room for improvement (Bone et al. 1993). Patients who have no room for improvement or the risk of death is either too high or too low should not be admitted to the ICU (Afessa et al. 1992; Kollef et al. 1995; Paz et al. 1993). The admission of a patient to the ICU is based on diagnosis-related priority models and priority models associated with objective parameter standards (Nasraway et al. 1998; Task Force of the American College of Critical Care Medicine (ACCM) of the Society of Critical Care Medicine (SCCM) 1999).

Patient severity scales are important supplies of the medical and nursing staff and influence the treatment plan of patients. Their main use concerns outcome assessment, assessment of the quality of the provided medicine and nursing care, and they are important tools in the hands of scientists in conducting research and/or clinical studies. The scores derived from the patient severity scales influence the decisions of the medical staff to develop the patient's treatment (Rapsang and Shyam 2014). The use of these tools leads to the right decision-making by physicians, which leads to the improvement of the efficiency of the provided health services due to better use of the available financial resources and also better management of the available human resources (Moran et al. 2004; Vincent and Moreno 2010).

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The medical staff who will make the final decision in whether to admit a patient to the ICU or not is faced with a moral dilemma. This intensivist has to identify the best personalized treatment for a patient, weighing the advantages and disadvantages of hospitalization in the ICU, along with the respective advantages and disadvantages of treating the same patient in the ward. Each (ICU or ward) can be evaluated by the staff as ineffective, disproportionate, or even undesirable (Schneiderman et al. 1990).

Particular factors such as hospital management, medical directors of wards, nursing staff, patients themselves, and their relatives or caregivers directly affect the decision regarding the admission of the patient to the ICU or the continuation of the treatment in the ward. However, the final is made by the intensivist who is called for estimation after assessing the patient and obtaining all the necessary information from the doctors in the ward (Tallgren et al. 2005).

The aim of this study was to investigate the outcomes and survival rates of patients in Greek hospital wards after an emergency call for estimation by an intensivist.

2 Materials and Methods

This is a prospective observational study of patients treated in a hospital ward at the General Oncology Hospital "Oi Agioi Anargyroi" in Greece. A data recording form was used by the researchers in order to collect the needed data. The study sample consists of patients hospitalized in a hospital ward for one calendar year (2014), whose condition was evaluated by an intensivist in the afternoon or the night shift.

2.1 Tools

For the purposes of the study, data recording forms were completed by the investigators, as independent observers (not involved in patient care), recording the basic demographic data of each patient, maintaining anonymity in order to protect personal data, the reason for calling the ICU, the Karnofsky scale (Schag et al. 1984), and data on hospitalization in the ICU (when patients were admitted to the ICU). There was a retrospective evaluation of the nursing file in the ward, wherever it was available, regarding the last 24 hours before the call to the intensivist.

2.2 Statistical Analysis

Data analysis were conducted using IBM statistics SPSS 21 (IBM Corp., Armonk, NY, USA). Patient characteristics were described using mean ± standard deviation (SD) or median and count (percentage), as appropriate. To adjust

the confounding variables for patient's outcome, the independent variables with $P < 0.2$ were entered into the multivariate binary regression model using the backward strategy.

3 Results

A total of 115 patients (58.3% men and 41.7% women) of mean age 67.1 ± 13.8 years (range 27–92 years) evaluated by an intensivist were recorded. 28.7% of them were hospitalized in a surgical clinic, 67% were hospitalized in internal medicine clinics (oncology), and 4.3% of the patients were treated in the emergency department, the radiotherapy department or the radiology department. 73% of the patients had a decision of hospitalization in the ICU. Total survival was 49.6%. Of the 31 patients who did not enter the ICU in a total of 115 patients, 15 survived (13% of the 115 patients or 48.4% of the 31 patients not admitted to the ICU). Five of them had cardiac arrest that had not been recovered and died without entering the ICU or continued their hospitalization in the ward. The survival rates of the patients not admitted to the ICU and continued hospitalization at the ward was 57.7%. Of the 84 patients admitted to the ICU in a total of 115 patients, 42 survived (36.5% of the 115 patients or 50% of the 84 patients admitted to the ICU). Medical interventions were conducted to 93% of the patients. The main characteristics of the sample are presented in Table 1.

The vital signs such as systolic blood pressure, diastolic blood pressure, mean arterial pressure, temperature, and pulse rate (beats per minute) were recorded for each patient. The vital signs of the patients are given in Table 2.

Table 1 Patients' characteristics ($n = 115$)

	Variables	*N*	%
Gender	Male	67	58.3
	Female	48	41.7
Clinic	Surgical	33	28.7
	Medical (oncology)	77	67
	Other	5	4.3
	Total (115)	57/115	26,2
Survival	Patients not admitted to the ICU (31)	15/115 (15/31)	13 (48.4)
	Patients admitted to the ICU (84)	42/115 (42/84)	36.5 (50)
Karnofsky scale	≥80	1	0.9
	50–70	7	6.1
	≤40	107	93
Medical interventions	Yes	110	96.5
	No	4	3.5

Table 2 Patients' vital points

Vital signs	Mean ± SD (range)
Systolic blood pressure	114 ± 27,6 mmHg (40–170 mmHg)
Diastolic blood pressure	60.6 ± 17.8 mmHg (30–100 mmHg)
Mean arterial pressure	77.7 ± 21.6 mmHg (20–120 mmHg)
Temperature	36.9 ± 1.1 °C (35 °C–40 °C)
Pulse rate (beats per minute)	89.8/min ± 22.9 (30–150/min)

Table 3 Findings on evaluation by intensivists

Symptoms	*N* = 115	Sole finding
Cardiopulmonary arrest	9 (7.8%)	5/9 (4.3%)
HeHeart rate – bradycardia	3 (2.6%)	
Heart rate – tachycardia	32 (27.8%)	
Low blood pressure – shock	26 (22.6%)	
Tachypnea	35 (30.4%)	2/35 (1.7%)
Bradypnea	2 (1.7%)	
Oxygen disorders – desaturation	68 (59.1%)	10/68 (8.7%)
Irregular breathing	24 (22.6%)	
Life-threatening airway obstruction	17 (14.8%)	2/17 (1.7%)
Temperature – fever	27 (23.5%)	1/27 (0.8%)
Renal dysfunction – oliguria	21 (18.3%)	1/21 (0.8%)
Electrolyte disorders	32 (27.8%)	6/32 (5.2%)
Level of consciousness – coma	30 (26.1%)	4/30 (3.5%)
Epileptic seizures	0 (0%)	
		N = 31/115 (26.9%)
Total findings	326 (2.83 per patient)	31/326 (9.5% of the total findings)

Table 4 Factors influencing the patients' outcome (multivariate accounting regression)

Factor	*P*	*B*	OR	95% of OR
Systolic blood pressure	0.001	1.123	8.145	6.779–9.716
Mean arterial pressure	0.023	3.447	6.794	5.441–9.119
Cardiopulmonary arrest	0.001	−0.879	12.447	9.15–15.879
APACHE II	0.002	0.474	1.16	1.101–1.212
SOFA score	0.002	0.551	1.12	1.077–1.331

Findings such as cardiopulmonary arrest, heart rate – bradycardia, heart rate disorders – tachycardia, low blood pressure – shock, tachypnea, bradypnea, oxygen disorders – desaturation, irregular breathing, life-threatening airway obstruction, temperature – fever, renal dysfunction – oliguria, electrolyte disorders, level of consciousness – coma and epileptic seizures were also recorded for each patient (Table 3). Table 4 presents the factors influencing the patients' outcome.

4 Discussion

This study concerns 115 patients of both medical (67%) and surgical etiology of mixed origin who needed hospital treatment according to the Karnofsky scale (93%, <40). Their prediction based on the Karnofsky scale was poor (>90%). The majority of the patients (96.5%) needed medical procedures after the evaluation by physicians at the ward. The majority of patients (105/115) had affected vital signs, and only 10 (8.7%) patients had normal vital signs but had other disorders.

Of the 11 patients who were not admitted to the ICU and did not survive, 8 were end-stage patients with irreversibility of the underlying disease, so it was established that they wouldn't benefit from ICU admission. Thus, it was not considered appropriate to introduce them into the ICU but to instead apply palliative relief therapy. It should be noted that 3 out of the 11 patients who had died had been intubated and put on mechanical breathing but were not transferred to the ICU because there were no available beds. The remaining 15 patients, out of the 26 who remained in the hospital ward and survived, were provisionally considered to have no need for hospitalization in the ICU because their condition was not evaluated as very serious and the disorders they presented could be managed in a ward with appropriate treatment and follow-up care.

Literature shows a limited number of research studying the outcomes and survival rates of patients in hospital wards in Greece after an emergency call for estimation by an intensivist. Oerlemans et al. (2015) conducted a study in the Netherlands aiming at assessing the moral dilemmas medical and nursing staff face during the decision-making process for transferring or releasing a patient to and from the ICU, respectively. This was a descriptive study with qualitative characteristics for the needs of which they conducted interviews. According to the results of this study, moral problems in the context of ICU entry and release can be divided into problems regarding the lack of ICU beds and the problems associated with the decisions regarding the treatment of the patient. Also, the gap between the high level of care that ICU can provide and the lower level of care provided in the general ward can sometimes lead to mutual misunderstandings between ICU staff and the cabin. The results of this study also show that when professionals from different clinics feel that there is a collective responsibility and effort in dealing with the patient, a reduction or even complete prevention of anxiety occurs. Researchers, therefore, conclude that it is important for ICU and cabin staff to communicate and cooperate effectively as there is mutual dependence on optimal patient flow between the various departments of the hospital. Interventions that improve understanding and cooperation can help mitigate moral problems and improve care by making the right decisions for the patients (Oerlemans et al. 2015).

Orsini et al. (2014) conducted a monocentric prospective observational study to assess the management of prospective patients to be admitted to the ICU during periods of lack of ICU available beds. According to these researchers, the decision to admit an ICU patient does not seem to be related to the number of available ICU beds in the hospital. A major factor that ultimately determined the decision to admit a

patient in the ICU was the severity of his condition, as expressed by the APACHE II scale. Orsini et al. (2014) suggested the development of special chambers for dealing with severely ill patients when beds in the ICU are occupied (Orsini et al. 2014).

Torke et al. (2014) studied the scope of decisions and the outcome of hospitalized elderly patients. According to the results of their study, various decisions were made after collaboration between the medical and nursing staff of the hospital and the family or caregivers of the patient. Researchers point out that each hospital should have the potential to treat its patients both in the ICU and in the ward, as various factors affect the admission of the elderly to the ICU (Torke et al. 2014).

4.1 Limitations

The main limitations of the present study are the relatively small sample size and the fact that the study was conducted in only one hospital. These limitations prevent the investigation of correlations between various research parameters and especially demographic and personal data referring to similar studies. Furthermore, the characteristics of our own hospital do not resemble other hospitals in the country due to the oncology character of the hospital. Staffing, the nature of patients who are mostly oncology patients, the experience of on-call doctors (that is small), and the training of nurses are additional factors that may have affected the results of our study.

5 Conclusions

The survival rates of the patients at risk in the ward are quite low and possibly multifactorial due to the severity of the disease, the unnecessary call for an intensivist due to an irreversible condition, or the delayed call for an intensivist. Better communication between the patients and the close family environment is required. Information regarding not only the patients' condition but also the severity, the prognosis, and the possible worsening as well as concerning the development of complications should be provided. In these cases, health-care professionals need to be informed about the patients' wishes regarding their desire to be admitted in the ICU and their wishes regarding life-ending situations. The training of qualified doctors on-call is very important in order to avoid unnecessary calls that burden the workload of intensivists.

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