Surg Today (2015) 45:259–270
DOI 10.1007/s00595-014-0863-y

REVIEW ARTICLE

The impact of aging on morbidity and mortality after liver resection: a systematic review and meta-analysis

Toru Mizuguchi · Masaki Kawamoto · Makoto Meguro · Kenji Okita · Shigenori Ota · Masayuki Ishii · Tomomi Ueki · Toshihiko Nishidate · Yasutoshi Kimura · Tomohisa Furuhata · Koichi Hirata

Received: 21 August 2013 / Accepted: 26 December 2013 / Published online: 14 February 2014

Abstract Surgery involving elderly patients is becoming increasingly common due to the rapid aging of societies all over the world. The objective of this study was to elucidate the prognostic differences between elderly and young patients who undergo liver resection. A systematic review based on the PRISMA flow diagram was conducted. Ovid Medline and PubMed were used to search for relevant literature published between January 2000 and March 2013, and the modified MINORS score was used to assess the methodological quality. In cases of hepatocellular carcinoma and miscellaneous liver tumors, the morbidity and mortality rate did not differ significantly between the elderly and young patients. For patients with colorectal metastatic liver cancer, the mortality of the young patients was 2.7 times lower than that of elderly patients. Our review of high-quality retrospective studies was able to elucidate the clinical risks of age on the outcomes after liver surgery in specific patient populations.

Keywords Aged patients · Elderly patients · Liver resection · Morbidity · Mortality

Introduction

During the last half century, life expectancy has been rising all over the world, which has resulted in increases in the frequency of surgery involving elderly patients [1, 2]. However, aging causes various physiological alterations, such as tissue fragility, metabolic dysfunction and deterioration of the immune response [3]. Although surgical outcomes have also improved during the last half century [4–6], the risks associated with surgery in elderly patients have not been fully elucidated.

Liver resection is often used to treat malignant tumors such as hepatocellular carcinoma, cholangiocellular carcinoma and metastatic liver cancer (e.g., from colorectal cancer) [7, 8]. The mortality rate of liver resection was reported to be less than a few percent in recent reports [9–12], although the morbidity rate was reported to range from 20 to 30 % [13–16]. The surgical outcomes of liver resection are largely dependent on the complexity of the procedure and the host liver function [8, 17]. Hepatocellular carcinoma usually develops in damaged livers, such as those of chronic hepatitis and liver cirrhosis patients, whose liver function has already deteriorated [17]. The histological background of the liver and liver function might also differ between young and old patients, which could affect the surgical outcomes. In addition, although metastatic liver tumors can develop in normal liver tissue, elderly patients often possess physiological defects that might make them more susceptible to adverse outcomes.

In this systematic review and meta-analysis, we searched the literature published from January 2000 to March 2013 to minimize the historical bias. Although a selection bias is inevitable during the selection of elderly patients, we considered that performing a cumulative meta-analysis might be the only strategy that would provide clear data on the outcomes of liver resection that would allow us to assess the effects of aging on such outcomes. Furthermore, as we considered that it was unlikely that there would be many randomized controlled trials (RCT) comparing the

T. Mizuguchi (✉) · M. Kawamoto · M. Meguro · K. Okita · S. Ota · M. Ishii · T. Ueki · T. Nishidate · Y. Kimura · T. Furuhata · K. Hirata
Department of Surgery I, Sapporo Medical University School of Medicine, Sapporo Medical University Hospital, Sapporo Medical University, S-1, W-16, Chuo-Ku, Sapporo, Hokkaido 060-8543, Japan
e-mail: tmizu@sapmed.ac.jp

outcomes of liver resection in young and old patients, we selected the studies using the Methodological Index for Non-Randomized Studies (MINORS) scoring system [18]. The aim of this study was to examine the effects of aging on the outcome of liver resection by reviewing relevant papers published since 2000.

Patients and methods

Study selection (Fig. 1)

The methodology used for this study adhered to the guidelines outlined in the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) statement (Fig. 1); [19, 20]. A search of all the published comparative studies, including evidence-based medicine reviews, examining the outcomes of young and old patients who underwent liver resection for malignant tumors was carried out using the PubMed and Ovid Medline databases. Studies that were published from January 2000 to March 2013 were reviewed, and the following "MeSH" search terms were used: "liver resection" and "hepatectomy." In addition, the following text filters were applied: "elderly", "aged" and "young". Duplicate and non-English or non-human studies were excluded.

As a result, 24 full papers were extracted and had their eligibility assessed. All of the studies were non-randomized studies, and therefore, were evaluated using the modified MINORS scoring system [18]. Of the 24 papers, 16 met our selection criteria, and were included in the final analysis. Among these 16 studies, five examined patients with hepatocellular carcinoma (HCC) (Table 1); [9–12, 21], six investigated patients with colorectal metastatic (CRM) cancer (Table 2) [13–16, 22, 23] and five focused on patients with miscellaneous tumors (Table 3); [24–28].

Data extraction

Two reviewers (T.M. and M.K.) independently extracted the following parameters from each study: first author, year of publication, study population characteristics, study design, inclusion and exclusion criteria and matching criteria. There was 100 % agreement between the two reviewers.

Inclusion criteria

To be included in the analysis, each study had to have: (1) compared the outcomes of young and old patients who underwent liver resection for malignant tumors, (2) involved human subjects, (3) reported morbidity and mortality data, (4) been written in English and (5) been published in 2000 or later.

Exclusion criteria

Studies were excluded from the analysis if: (1) the outcomes of interest were not clearly reported, (2) it was impossible to extract or calculate the appropriate data from the published results, (3) they displayed considerable

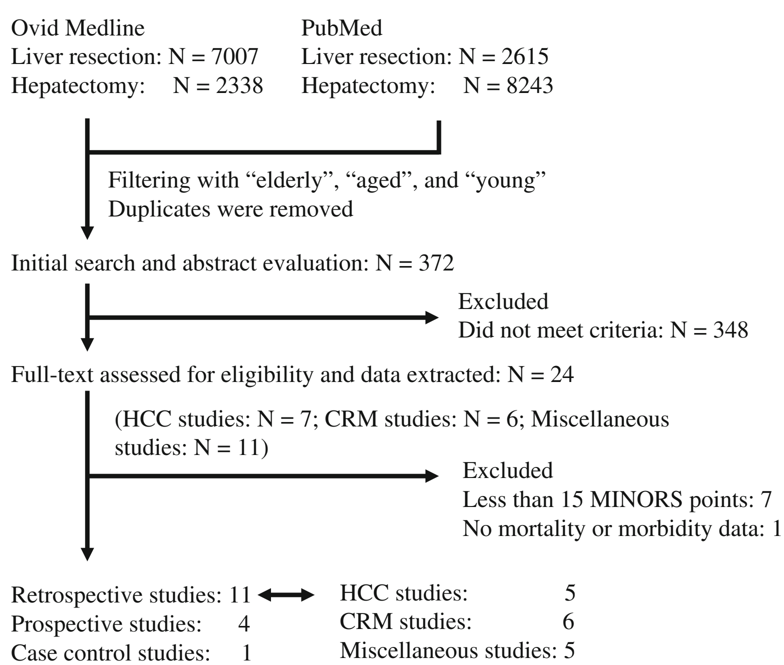


Fig. 1 A flow chart showing how we conducted the literature search and the quality appraisal prior to the meta-analysis. A total of 16 studies were extracted based on our inclusion and exclusion criteria from among 24 full-text studies that met our Methodological Index for Non-Randomized Studies (*MINORS*) score criterion

Table 1 Characteristics and quality assessment scores of studies comparing young and old patients who underwent liver resection for hepatocellular carcinoma

No.	First author	Year	Number		Mean or median age (years)		Age criterion	Morbidity (%)		Mortality (%)		Single tumor (%)		Major resection (%)		MINORS score
			Young	Old	Young	Old		Young	Old	Young	Old	Young	Old	Young	Old	
#1	Hanazaki	2000	283	103	59.6	73.1	≥70	23.3	28.2	9.9	14.6	51.2	45.6	16.3	15.5	16
#2	Ferrero	2005	177	64	60.9	74.4	≥71	42.4	23.4	9.6	3.1	76.8	81.3	20.9	31.3	15
#3	Huang	2009	268	67	48.1	72.3	≥70	4.5	8.9	1.1	1.5	70.1	77.6	20.5	16.4	15
#4	Potolani	2011	276	175	60.8	75.2	≥70	44.6	50.9	4.3	3.4	75.7	72.0	21.7	17.1	15
#5	Lee	2012	90	61	35.1	72.6	≥70	14.4	27.9	–	–	76.7	85.2	41.1	57.4	15

MINORS Modified methodological index of non-randomized studies, *HCC* hepatocellular carcinoma, *NA* not applicable, – not described

Table 2 Characteristics and quality assessment scores of studies comparing young and old patients who underwent liver resection for colorectal metastatic liver cancer

No.	First author	Year	Number		Mean or median age (years)		Age criterion	Morbidity (%)		Mortality (%)		Single tumor (%)		Major resection (%)		MINORS score
			Young	Old	Young	Old		Young	Old	Young	Old	Young	Old	Young	Old	
#6	Nagano	2005	150	62	58.3	74.2	≥71	23.3	19.4	0.7	0	62.0	54.8	37.3	32.3	16
#7	Mazzoni	2007	144	53	57.8	73.9	≥70	33.3	20.8	2.1	5.7	45.1	54.7	17.4	20.8	16
#8	Adam	2010	6140	1624	–	–	≥70	28.7	32.3	1.6	3.8	64.0	75.2	42.6	37.6	19
#9	Benedetto	2011	32	32	59.4	73.6	≥70	34.4	28.1	0	3.1	59.4	59.4	62.5	59.4	15
#10	Kulik	2011	719	190	–	–	≥70	13.9	11.6	1.3	0.5	51.0	55.8	48.4	43.2	17
#11	Cook	2012	1292	151	62	77	≥75	21.2	32.5	1.3	7.3	39.2	45.7	60.8	54.3	20

MINORS Modified methodological index of non-randomized studies

overlap with another study with regard to the authors, centers or patient cohorts evaluated.

Outcomes of interest and definitions

The following outcomes were compared between the young and old patients: the type of liver tumor, morbidity, mortality and the frequencies of single tumors and major resections.

Statistical analysis

A meta-analysis was carried out using the MedCalc software package (Ver 8.0.1.0, Mariakerke, Belgium) and a comprehensive meta-analysis software package (Biostat, Englewood, NJ). Statistical analyses of dichotomous variables were carried out using odds ratios (OR) as a summary statistic, and the data were reported together with 95 % confidence intervals (CI). The odds ratios reported in this paper represent the odds of an adverse event occurring in the old group compared with the young group. The Mantel–Haenszel method was used to combine the OR for the outcomes of interest using the "random effect" meta-analytical technique. Heterogeneity was assessed by graphic exploration, with funnel plots used to evaluate the publication bias.

Results

We reviewed comparative studies published since 2000 involving young and old patients who underwent liver resection, as described in the Methods section (Fig. 1). All studies that achieved less than 15 MINORS points were excluded; hence, a total of 16 studies were analyzed in this study [29–36]. The target tumors in each study were HCC in five studies (Table 1), CRM in six studies (Table 2) and miscellaneous tumors in five studies (Table 3).

Meta-analysis of the HCC studies

Although none of the five HCC studies were RCT [9–12, 21], one of the excluded studies included a propensity score

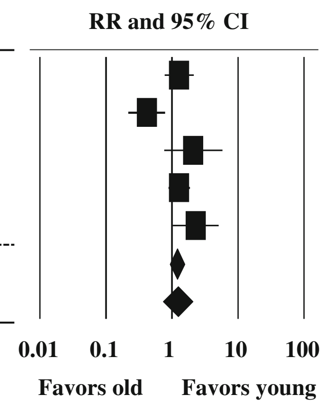
Table 3 Characteristics and quality assessment scores of studies comparing young and old patients who underwent liver resection for miscellaneous mixed liver tumors, including primary liver cancer and secondary liver cancer

No.	First author	Year	Number		Mean or median age (years)		Age criterion	Morbidity (%)		Mortality (%)		Major resection (%)	
			Young	Old	Young	Old		Young	Old	Young	Old	Young	Old
#12	Cescon	2003	99	23	57	73	≥70	32.3	39.1	2.0	0	100	100
#13	Menon	2006	390	127	57	73	≥70	32.8	30.7	5.4	7.9	100	100
#14	Shirabe	2009	307	43	–	82	≥80	21.8	25.6	0.7	0	19.2	16.3
#15	Reddy	2011	749	107	–	–	≥75	46.5	51.4	5.9	8.4	100	100
#16	Melloul	2012	64	23	57	75	≥70	37.5	52.2	3.1	8.7	100	100

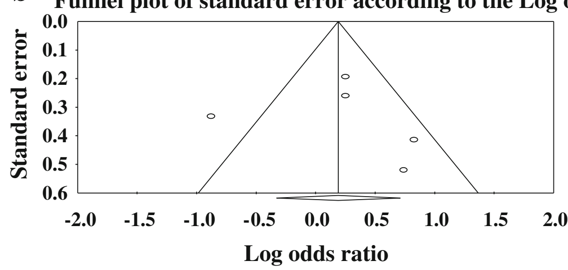
MINORS Modified methodological index of non-randomized studies

a

Study	Old	Young	Odds	95% CI	Z-value	P-value
Hanazaki	29/103	66/283	1.288	0.774 to 2.146	0.974	0.330
Ferrero	15/64	75/177	0.416	0.217 to 0.798	-2.640	0.008
Huang	6/67	12/268	2.098	0.757 to 5.813	1.426	0.154
Potolani	89/175	123/276	1.287	0.881 to 1.882	1.304	0.192
Lee	17/61	13/90	2.288	1.016 to 5.152	1.999	0.046
Total (fixed effects)	156/470	289/1094	1.153	0.899 to 1.479	1.302	0.193
Total (random effects)	156/470	289/1094	1.210	0.720 to 2.033	0.722	0.471



b Funnel plot of standard error according to the Log odds ratio



Test for heterogeneity
Q: 13.988
DF: 4
Significance level: P = 0.007

Fig. 2 An annotated forest plot obtained via a meta-analysis of the morbidity in old vs. young hepatocellular carcinoma (*HCC*) patients (**a**). A Mantel–Haenszel fixed-effects model and random-effects model were used for the meta-analysis. The odds ratios (*Odds*) are shown together with 95 % confidence intervals (*CI*). An annotated funnel plot of the SE according to the log odds ratio for the meta-analysis of young vs. old HCC patients (**b**). *Open circles* show the original data, and the *diamond* below the figure indicates the overall mean, as well as the 95 % CI, of the standardized mean difference. The *P* values are for the heterogeneity test

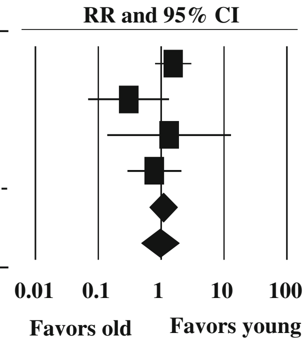
matching-based analysis, which did not detect any differences in the clinical outcomes between the young and old patients [30]. The morbidity in the five included studies did not differ significantly between the old and young patients (Fig. 2a, $P = 0.471$), although heterogeneity was detected among the studies (Fig. 2b, $P = 0.007$). No differences in the mortality rates were detected between the groups (Fig. 3, $P = 0.888$), and the test for heterogeneity was negative (Fig. 3b, $P = 0.219$). The frequencies of single tumors (Fig. 4a, $P = 0.774$) and major hepatectomy (Fig. 5a, $P = 0.630$) did not differ significantly among the groups, and no heterogeneity was detected among the studies (Figs. 4b, $P = 0.251$; 5b, $P = 0.079$).

Meta-analysis of the colorectal metastatic liver cancer (CRM) studies

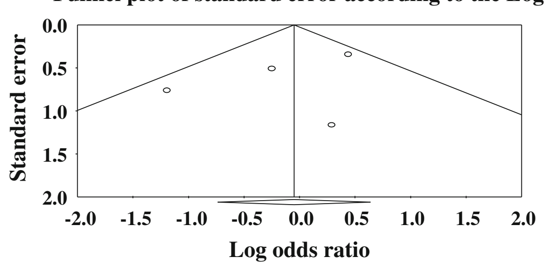
A total of six studies of CRM were eligible for the final meta-analysis (Table 2); [13–16, 22, 23]. The morbidity rate of the CRM patients did not differ significantly among

a

Study	Old	Young	Odds	95% CI	Z-value	P-value
Hanazaki	15/103	28/283	1.552	0.793 to 3.041	1.282	0.200
Ferrero	2/64	17/177	0.304	0.0681 to 1.353	-1.564	0.118
Huang	1/67	3/268	1.338	0.137 to 13.075	0.251	0.802
Potolani	6/175	12/276	0.781	0.288 to 2.121	-0.485	0.628
Total (fixed effects)	24/409	60/1004	0.981	0.597 to 1.610	0.247	0.805
Total (random effects)	24/409	60/1004	0.947	0.472 to 1.902	-0.141	0.888



b

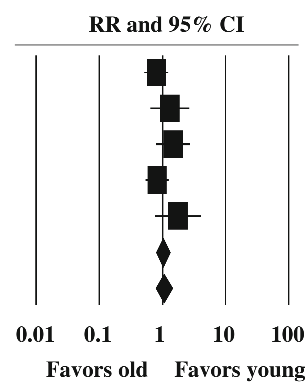


Test for heterogeneity
Q: 4.429
DF: 3
Significance level: P = 0.219

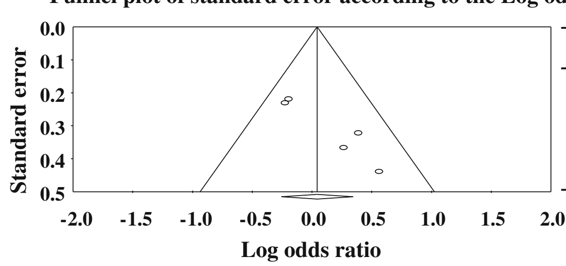
Fig. 3 An annotated forest plot obtained via a meta-analysis of mortality in old vs. young hepatocellular carcinoma (*HCC*) patients (**a**). A Mantel–Haenszel fixed-effects model and random-effects model were used for the meta-analysis. The odds ratios (*Odds*) are shown together with the 95 % confidence intervals (*CI*). An annotated funnel plot of the SE according to the log odds ratio for the meta-analysis of young vs. old HCC patients (**b**). The *open circles* are the original data, and the *diamond* below the figure indicates the overall mean, as well as the 95 % CI, of the standardized mean difference. The *P* values are for the heterogeneity test

a

Study	Old	Young	Odds	95% CI	Z-value	P-value
Hanazaki	47/103	145/283	0.799	0.508 to 1.256	-0.973	0.330
Ferrero	52/64	136/177	1.306	0.637 to 2.679	0.729	0.466
Huang	52/67	188/268	1.475	0.785 to 2.773	1.207	0.227
Potolani	126/175	209/276	0.824	0.536 to 1.267	-0.881	0.378
Lee	52/61	69/90	1.758	0.744 to 4.155	1.287	0.198
Total (fixed effects)	329/470	747/1094	1.015	0.794 to 1.299	0.055	0.956
Total (random effects)	329/470	747/1094	1.045	0.775 to 1.409	0.287	0.774



b

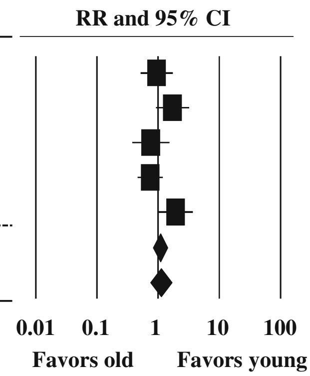


Test for heterogeneity
Q: 5.369
DF: 4
Significance level: P = 0.251

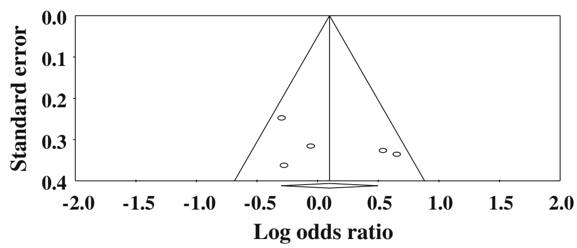
Fig. 4 An annotated forest plot obtained via a meta-analysis of the frequency of single tumors in old vs. young hepatocellular carcinoma (*HCC*) patients (**a**). A Mantel–Haenszel fixed-effects model and random-effects model were used for the meta-analysis. The odds ratios (*Odds*) are shown together with the 95 % confidence intervals (*CI*). An annotated funnel plot of the SE according to the log odds ratio for the meta-analysis of young vs. old HCC patients (**b**). The *open circles* are the original data, and the *diamond* below the figure indicates the overall mean, as well as the 95 % CI, of the standardized mean difference. The *P* values are for the heterogeneity test

a

Study	Old	Young	Odds	95% CI	Z-value	P-value
Hanazaki	16/103	46/283	0.948	0.510 to 1.761	-0.170	0.865
Ferrero	20/64	37/177	1.720	0.906 to 3.264	1.659	0.097
Huang	11/67	55/268	0.761	0.374 to 1.549	-0.754	0.451
Potolani	30/175	60/276	0.745	0.458 to 1.211	-1.188	0.235
Lee	35/61	37/90	1.928	0.998 to 3.726	1.954	0.051
Total (fixed effects)	112/470	235/1094	1.060	0.811 to 1.384	0.483	0.629
Total (random effects)	112/470	235/1094	1.103	0.741 to 1.642	0.482	0.630



b Funnel plot of standard error according to the Log odds ratio

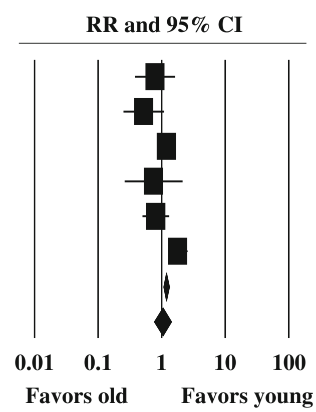


Test for heterogeneity
Q: 8.349
DF: 4
Significance level: P = 0.079

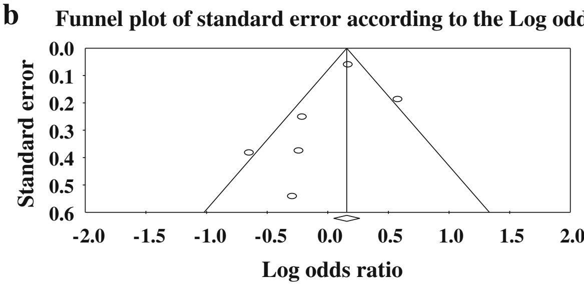
Fig. 5 An annotated forest plot obtained via a meta-analysis of the frequency of major hepatectomy in old vs. young hepatocellular carcinoma (*HCC*) patients (**a**). A Mantel–Haenszel fixed-effects model and random-effects model were used for the meta-analysis. The odds ratios (*Odds*) are shown together with the 95 % confidence intervals (*CI*). An annotated funnel plot of the SE according to the log odds ratio for the meta-analysis of young vs. old HCC patients (**b**). The *open circles* are the original data, and the *diamond* below the figure indicates the overall mean, as well as the 95 % CI, of the standardized mean difference. The *P* values are for the heterogeneity test

a

Study	Old	Young	Odds	95% CI	Z-value	P-value
Nagano	12/62	35/150	0.789	0.378 to 1.644	-0.633	0.526
Mazzoni	11/53	48/144	0.524	0.248 to 1.108	-1.692	0.091
Adam	524/1624	1762/6140	1.184	1.052 to 1.332	2.804	0.005
Benedetto	9/32	11/32	0.747	0.259 to 2.159	-0.539	0.590
Kulik	22/190	100/719	0.811	0.496 to 1.326	-0.836	0.403
Cook	49/151	274/1292	1.785	1.238 to 2.573	3.103	0.002
Total (fixed effects)	175/2112	652/8477	1.169	1.051 to 1.300	2.871	0.004
Total (random effects)	175/2112	652/8477	1.024	0.751 to 1.396	0.150	0.881



b Funnel plot of standard error according to the Log odds ratio

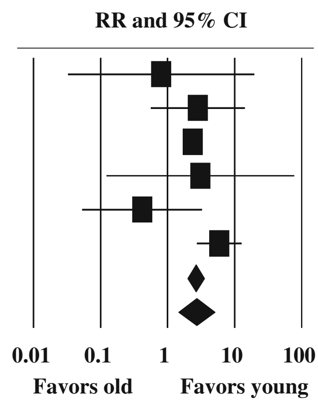


Test for heterogeneity
Q: 13.525
DF: 5
Significance level: P = 0.019

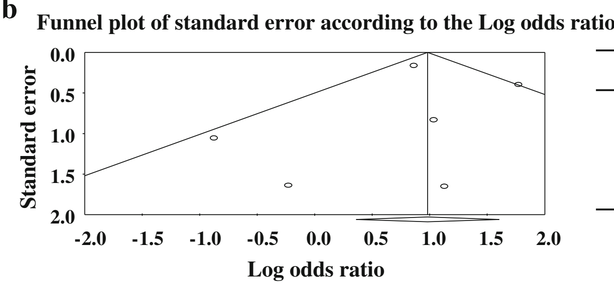
Fig. 6 An annotated forest plot obtained via a meta-analysis of the morbidity in old vs. young colorectal metastatic liver cancer (*CRM*) patients (**a**). A Mantel–Haenszel fixed-effects model and random-effects model were used for the meta-analysis. The odds ratios (*Odds*) are shown together with the 95 % confidence intervals (*CI*). An annotated funnel plot of the SE according to log odds ratio for the meta-analysis of young vs. old CRM patients (**b**). The *open circles* are the original data, and the *diamond* below the figure indicates the overall mean, as well as the 95 % CI, of the standardized mean difference. The *P* values are for the heterogeneity test

a

Study	Old	Young	Odds	95% CI	Z-value	P-value
Nagano	0/62	1/150	0.797	0.032 to 19.841	-0.138	0.890
Mazzoni	3/53	3/144	2.820	0.551 to 14.429	1.245	0.213
Adam	62/1624	101/6140	2.373	1.722 to 3.272	5.276	0.000
Benedetto	1/32	0/32	3.095	0.121 to 78.872	0.684	0.494
Kulik	1/190	9/719	0.417	0.0526 to 3.315	-0.826	0.409
Cook	11/151	17/1292	5.893	2.706 to 12.833	4.467	0.000
Total (fixed effects)	78/2112	131/8477	2.451	1.845 to 3.257	6.513	0.000
Total (random effects)	78/2112	131/8477	2.662	1.419 to 4.996	3.102	0.002



b



Test for heterogeneity
Q: 8.240
DF: 5
Significance level: P = 0.143

Fig. 7 An annotated forest plot obtained via a meta-analysis of mortality in old vs. young colorectal metastatic liver cancer (*CRM*) patients (**a**). A Mantel–Haenszel fixed-effects model and random-effects model were used for the meta-analysis. The odds ratios (*Odds*) are shown together with the 95 % confidence intervals (*CI*). An annotated funnel plot of the SE according to the log odds ratio for the meta-analysis of young vs. old CRM patients (**b**). The *open circles* are the original data, and the *diamond* below the figure indicates the overall mean, as well as the 95 % CI, of the standardized mean difference. The *P* values are for the heterogeneity test

the groups (Fig. 6a, $P = 0.881$), although heterogeneity was detected among the studies (Fig. 6b, $P = 0.019$). However, the mortality rate of the old patients was significantly higher than that of the young patients (Fig. 7a, OR: 2.662, $P = 0.002$), and the test for heterogeneity was negative (Fig. 7b, $P = 0.143$). Single tumors were significantly more common among the old patients than the young patients (Fig. 8a, OR: 1.310, $P = 0.049$), but heterogeneity was detected among the studies (Fig. 8b, $P = 0.033$). Conversely, the old patients underwent major hepatectomy significantly less frequently than did the young patients (Fig. 9a, OR: 0.812, $P = 0.000$), and no heterogeneity was detected among the studies (Fig. 9b, $P = 0.938$).

Meta-analysis of miscellaneous mixed tumors, including primary liver cancer and secondary liver cancer

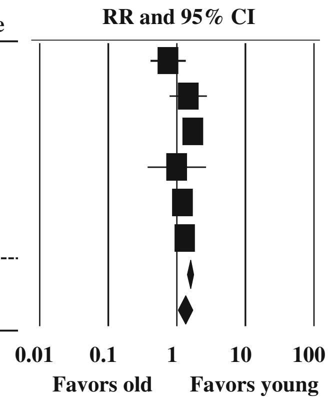
A total of five studies of miscellaneous mixed tumors were eligible for the final meta-analysis (Table 3); [24–28]. In this group, all but one of the studies compared the clinical outcomes between old and young patients following major hepatectomy. The morbidity (Fig. 10a, $P = 0.307$) and mortality (Fig. 11a, $P = 0.103$) rates did not differ significantly among the old and young patients, and the test for heterogeneity was negative (Figs. 10b: $P = 0.691$ and 11b: $P = 0.965$, respectively).

Discussion

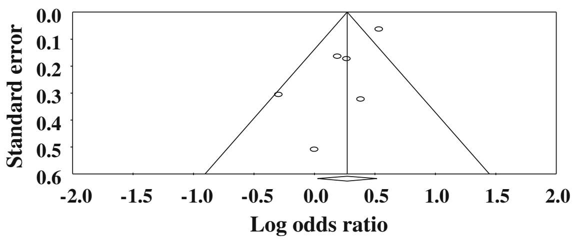
We reviewed comparative studies published since 2000 involving old and young patients who underwent hepatectomy for various tumors and evaluated their findings in a meta-analysis. In addition, we also conducted the funnel plot analyses to determine the degree of heterogeneity among the studies analyzed. Although neither the morbidity nor mortality rate of the HCC patients and miscellaneous mixed tumor patients differed significantly among the old and young patients, those of the CRM patients differed among the age groups. This meta-analysis suggests that older age is associated with increased risks after liver resection in patients with CRM.

a

Study	Old	Young	Odds	95% CI	Z-value	P-value
Nagano	34/62	93/150	0.744	0.409 to 1.355	-0.966	0.334
Mazzoni	29/53	65/144	1.469	0.780 to 2.765	1.191	0.234
Adam	1222/1624	3931/6140	1.708	1.509 to 1.934	8.452	0.000
Benedetto	19/32	19/32	1.000	0.369 to 2.712	0.000	1.000
Kulik	106/190	367/719	1.210	0.878 to 1.669	1.164	0.245
Cook	69/151	506/1292	1.307	0.931 to 1.835	1.548	0.122
Total (fixed effects)	1479/2112	4981/8477	1.554	1.399 to 1.726	8.088	0.000
Total (random effects)	1479/2112	4981/8477	1.310	1.026 to 1.674	2.165	0.049



b Funnel plot of standard error according to the Log odds ratio



Test for heterogeneity
Q: 12.134
DF: 5
Significance level: P = 0.033

Fig. 8 An annotated forest plot obtained via a meta-analysis of the frequency of single tumors in old vs. young colorectal metastatic liver cancer (*CRM*) patients (**a**). A Mantel–Haenszel fixed-effects model and random-effects model were used for the meta-analysis. The odds ratios (*Odds*) are shown together with the 95 % confidence intervals (*CI*). An annotated funnel plot of the SE according to the log odds ratio for the meta-analysis of young vs. old CRM patients (**b**). The *open circles* are the original data, and the *diamond* below the figure indicates the overall mean, as well as the 95 % CI, of the standardized mean difference. The *P* values are for the heterogeneity test

Definition of elderly patients

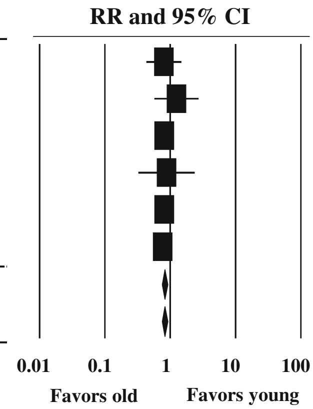
The definition of old patients varied among the reports. However, the cut-off age used in all of the HCC studies [9–12, 21], five of the six CRM studies [13–15, 22, 23] and three of the five miscellaneous tumor studies was 70 years old [24, 25, 28]. Although Melloul et al. [28] also found that there was no clear cut-off age for defining old patients, most studies published after 2000 defined old patients as those aged 70 years and over. The effect of aging on liver function is largely unknown, but the size of the liver and hepatic blood flow were previously to have negative correlations with age [13, 37, 38]. Although aging has inevitable physiological effects, a cut-off age of 70 might not be old enough to detect marked clinical effects of aging. The ideal cut-off age for examining the effect of aging might be ≥75 [16], but studies that use such cut-off values might have insufficient statistical power to detect clinical effects due to the limited numbers of patients that can be recruited, which likely explains why a cut-off age of 70 has been used in many studies of liver resection. If we could recruit a sufficient number of patients aged ≥75 years as elderly patients, we might obtain different results and see more marked effects of aging on the surgical outcomes.

Differences in the morbidity and mortality rates based on the tumor type

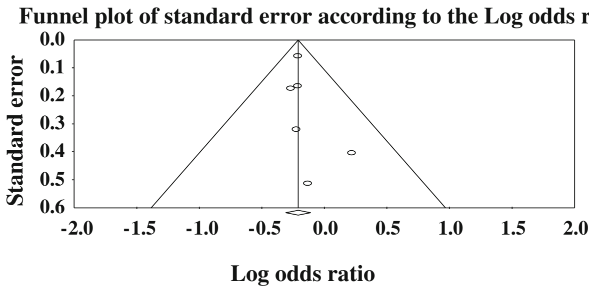
One of the interesting findings of this study was the differences among the various types of tumors. Although the morbidity and mortality rates of HCC and the miscellaneous tumors did not differ significantly between the young and old patients, those of CRM did. In the CRM analysis, it was found that the old patients exhibited a higher number of tumors, but underwent major hepatectomy less often than did the young patients. Therefore, in the cases of CRM, the higher mortality rate of the old patients might be related to tumor progression, rather than the extent of hepatectomy. On the other hand, in the cases of HCC, neither the number of tumors nor the percentage of patients selected for major hepatectomy differed between the groups. Therefore, the similarities in the oncological characteristics and surgical approaches of these cases might have resulted in the similar clinical outcomes seen in the two age groups. Another possible reason is that the mortality rate varies among the different types of tumors. The mean mortality rate of HCC was around 5–10 %, whereas that of CRM was only a few percent for the young patients and around 5 % for the old patients. The higher mortality rate of HCC might be associated with damage to

a

Study	Old	Young	Odds	95% CI	Z-value	P-value
Nagano	20/62	56/150	0.799	0.427 to 1.496	-0.700	0.484
Mazzoni	11/53	25/144	1.247	0.565 to 2.751	0.546	0.585
Adam	610/1624	2617/6140	0.810	0.724 to 0.906	-3.676	0.000
Benedetto	19/32	20/32	0.877	0.321 to 2.396	-0.256	0.798
Kulik	82/190	348/719	0.809	0.586 to 1.117	-1.286	0.198
Cook	82/151	786/1292	0.765	0.545 to 1.074	-1.548	0.122
Total (fixed effects)	824/2112	3852/8477	0.812	0.735 to 0.896	-4.141	0.000
Total (random effects)	824/2112	3852/8477	0.812	0.735 to 0.896	-4.141	0.000



b



Test for heterogeneity
Q: 1.273
DF: 5
Significance level: P = 0.938

Fig. 9 An annotated forest plot obtained via a meta-analysis of the frequency of major hepatectomy in old vs. young colorectal metastatic liver cancer (*CRM*) patients (**a**). A Mantel–Haenszel fixed-effects model and random-effects model were used for the meta-analysis. Odds ratios (*Odds*) are shown together with the 95 % confidence intervals (*CI*). An annotated funnel plot of the SE according to the log odds ratio for the meta-analysis of young vs. old CRM patients (**b**). The *open circles* are the original data, and the *diamond* below the figure indicates the overall mean, as well as the 95 % CI, of the standardized mean difference. The *P* values are for the heterogeneity test

the liver itself, e.g., due to chronic hepatitis or liver cirrhosis [5]. Although minor resections were preferred for HCC management, the risks associated with poor liver function might outweigh the age-related risk factors. Our meta-analysis clearly demonstrated that the clinical outcomes differed among the examined tumor types; however, the reason for these differences remains unclear.

Indications for hepatectomy in elderly patients

Age itself has never been considered a valid reason to change the basic surgical indications for any tumor [16, 22], although the mortality and morbidity rates of old patients might be higher than those of young patients. The evaluation and management of co-existing co-morbidities, which tend to become more common with age, plays a major role in achieving positive clinical outcomes [22]. Even in 75-year-old patients, survival for 2 years would be unlikely without surgical resection. Therefore, the surgical indications for old patients largely depend on their systemic physiological condition. The eligibility of elderly patients for liver resection should therefore be clarified in a future study by evaluating the effects of co-existing co-morbidities.

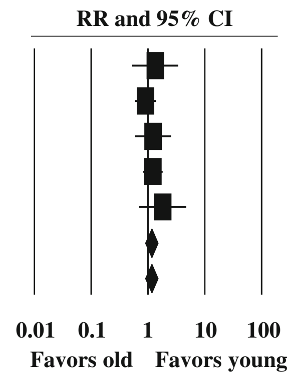
Besides the physiological condition, the psychological condition should be considered in the elderly patients. The risk factors for delirium have been reported to include an older age, poor liver function and advanced cancer stage [39]. Providing that an old patient is eligible for liver resection in terms of their physiological and psychological findings, a reasonable clinical outcome can be expected.

Implications for elderly patients who undergo hepatectomy

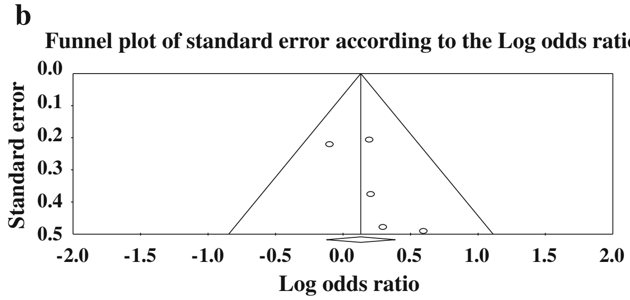
When interpreting the results of this meta-analysis, it is important to pay attention to the clinical profiles of each type of tumor. In HCC, the mean age of the old patients ranged from 72 to 75 years, whereas that of the young patients ranged from 35 to 60. In addition, the frequency of single tumors was 75 %, and that of major resection was about 20 %. On the other hand, in cases with CRM, the mean age of the old patients was between 73 and 77, whereas that of the young patients ranged from 57 to 62. The frequencies of single tumors and major hepatectomy

a

Study	Old	Young	Odds	95% CI	Z-value	P-value
Cescon	9/23	32/99	1.346	0.527 to 3.437	0.621	0.534
Menon	39/127	128/390	0.907	0.589 to 1.398	4.544	0.000
Shirabe	11/43	67/307	1.231	0.589 to 2.572	0.554	0.580
Reddy	55/107	348/749	1.219	0.813 to 1.828	0.957	0.339
Melloul	12/23	24/64	1.818	0.695 to 4.758	1.218	0.223
Total (fixed effects)	126/323	599/1609	1.139	0.885 to 1.467	1.021	0.307
Total (random effects)	126/323	599/1609	1.141	0.885 to 1.471	1.021	0.307



b

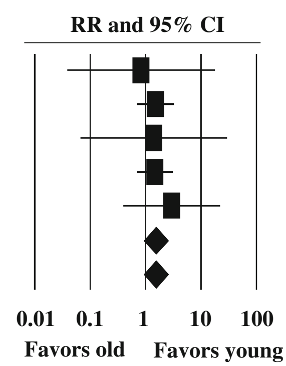


Test for heterogeneity
Q: 2.245
DF: 4
Significance level: P = 0.691

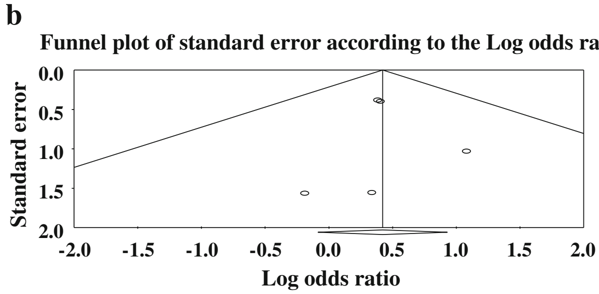
Fig. 10 An annotated forest plot obtained via a meta-analysis of the morbidity in old vs. young miscellaneous tumor patients (**a**). A Mantel–Haenszel fixed-effects model and random-effects model were used for the meta-analysis. Odds ratios (*Odds*) are shown together with the 95 % confidence intervals (*CI*). An annotated funnel plot of the SE according to the log odds ratio for the meta-analysis of young vs. old miscellaneous cancer patients (**b**). The *open circles* are the original data, and the *diamond* below the figure indicates the overall mean, as well as the 95 % CI, of the standardized mean difference. The *P* values are for the heterogeneity test

a

Study	Old	Young	Odds	95% CI	Z-value	P-value
Cescon	0/23	2/99	0.830	0.0385 to 17.869	-0.119	0.905
Menon	10/127	21/390	1.502	0.688 to 3.280	1.020	0.308
Shirabe	0/43	2/307	1.405	0.0663 to 29.747	0.218	0.827
Reddy	9/107	44/749	1.471	0.697 to 3.107	1.013	0.311
Melloul	2/23	2/64	2.952	0.391 to 22.290	1.050	0.294
Total (fixed effects)	21/323	71/1609	1.520	0.918 to 2.517	1.630	0.103
Total (random effects)	21/323	71/1609	1.525	0.918 to 2.532	1.630	0.103



b



Test for heterogeneity
Q: 0.574
DF: 4
Significance level: P = 0.965

Fig. 11 An annotated forest plot obtained via a meta-analysis of the mortality in old vs. young miscellaneous tumor patients (**a**). A Mantel–Haenszel fixed-effects model and random-effects model were used for the meta-analysis. The odds ratios (*Odds*) are shown together with 95 % confidence intervals (*CI*). An annotated funnel plot of the SE according to the log odds ratio for the meta-analysis of young vs. old miscellaneous cancer patients (**b**). The *open circles* are original data, and the *diamond* below the figure indicates the overall mean, as well as the 95 % CI, of the standardized mean difference. The *P* values are for the heterogeneity test

were both 50 %. Therefore, HCC patients who are aged ≤75 years are more likely to have single tumors, and are eligible for minor resection that can provide similar clinical outcomes after hepatectomy to those obtained in younger patients. On the other hand, the older CRM patients, who were around 75 years old, are at a 2.7fold higher risk of mortality than patients aged around 60 years old, regardless of the number of tumors and the type of liver resection.

In conclusion, we reviewed studies published since 2000 that compared the outcomes of young and old patients who underwent hepatectomy. The rapid growth of the aged population requires clinicians to examine the surgical risk profiles of old patients. The most important finding of our study is that the morbidity and mortality rates after hepatectomy differ according to tumor type. Therefore, the indications for hepatectomy for old patients should be based on the type of tumor. Future studies should focus on elucidating the effects of aging on the patients' systemic physiological profiles and the associations between these profiles and the oncological characteristics.

Acknowledgments This study was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan, No. 23591993 to T. Mizuguchi.

References

1. Centers for Disease Control and Prevention (CDC). Trends in aging—US and worldwide. MMWR Morb Mortal Wkly Rep. 2003;52:101–4.
2. From the Centers for Disease Control and Prevention. Public health and aging: trends in aging—US and worldwide. JAMA. 2003;289:1371–3.
3. Straub RH, Cutolo M, Zietz B, Scholmerich J. The process of aging changes the interplay of the immune, endocrine and nervous systems. Mech Age Dev. 2001;122:1591–611.
4. Nguyen KT, Marsh JW, Tsung A, Steel JJ, Gamblin TC, Geller DA. Comparative benefits of laparoscopic vs open hepatic resection: a critical appraisal. Arch Surg. 2011;146:348–56.
5. Mizuguchi T, Kawamoto M, Meguro M, Nakamura Y, Ota S, Hui TT, et al. Prognosis and predictors of surgical complications in hepatocellular carcinoma patients with or without cirrhosis after hepatectomy. World J Surg. 2013;37:1379–87.
6. Nanashima A, Abo T, Hamasaki K, Wakata K, Kunizaki M, Tou K, et al. Predictors of intraoperative blood loss in patients undergoing hepatectomy. Surg Today. 2013;43:485–93.
7. Shimada H, Tanaka K, Endou I, Ichikawa Y. Treatment for colorectal liver metastases: a review. Langenbecks Arch Surg. 2009;394:973–83.
8. Cauchy F, Fuks D, Belghiti J. HCC: current surgical treatment concepts. Langenbecks Arch Surg. 2012;397:681–95.
9. Hanazaki K, Kajikawa S, Shimozawa N, Mihara M, Shimada K, Hiraguri M, et al. Survival and recurrence after hepatic resection of 386 consecutive patients with hepatocellular carcinoma. J Am Coll Surg. 2000;191:381–8.
10. Ferrero A, Vigano L, Polastri R, Ribero D, Lo Tesoriere R, Muratore A, et al. Hepatectomy as treatment of choice for hepatocellular carcinoma in elderly cirrhotic patients. World J Surg. 2005;29:1101–5.
11. Huang J, Li BK, Chen GH, Li JQ, Zhang YQ, Li GH, et al. Long-term outcomes and prognostic factors of elderly patients with hepatocellular carcinoma undergoing hepatectomy. J Gastroint Surg. 2009;13:1627–35.
12. Portolani N, Baiocchi GL, Coniglio A, Tiberio GA, Prestini K, Gheza F, et al. Limited liver resection: a good indication for the treatment of hepatocellular carcinoma in elderly patients. Jpn J Clin Oncol. 2011;41:1358–65.
13. Nagano Y, Nojiri K, Matsuo K, Tanaka K, Togo S, Ike H, et al. The impact of advanced age on hepatic resection of colorectal liver metastases. J Am Coll Surg. 2005;201:511–6.
14. Mazzoni G, Tocchi A, Miccini M, Bettelli E, Cassini D, De Santis M, et al. Surgical treatment of liver metastases from colorectal cancer in elderly patients. Int J Colorect Dis. 2007;22:77–83.
15. Di Benedetto F, Berretta M, D'Amico G, et al. Liver resection for colorectal metastases in older adults: a paired matched analysis. J Am Geriatr Soc. 2011;59:2282–90.
16. Cook EJ, Welsh FK, Chandrakumaran K, Montalti R, De Ruvo N, Cautero N, et al. Resection of colorectal liver metastases in the elderly: does age matter? Colorect Dis. 2012;14:1210–6.
17. Mizuguchi T, Kawamoto M, Meguro M, Hui TT, Hirata K. Preoperative liver function assessments to estimate the prognosis and safety of liver resections. Surg Today. 2014;44:1–10.
18. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg. 2003;73:712–6.
19. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.
20. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700.
21. Lee CR, Lim JH, Kim SH, Ahn SH, Park YN, Choi GH, et al. A comparative analysis of hepatocellular carcinoma after hepatic resection in young versus elderly patients. J Gastroint Surg. 2012;16:1736–43.
22. Adam R, Frilling A, Elias D, Laurent C, Ramos E, Capussotti L, et al. Liver resection of colorectal metastases in elderly patients. Br J Surg. 2010;97:366–76.
23. Kulik U, Framke T, Grosshennig A, Ceylan A, Bektas H, Klempnauer J, et al. Liver resection of colorectal liver metastases in elderly patients. World J Surg. 2011;35:2063–72.
24. Cescon M, Grazi GL, Del Gaudio M, Ercolani G, Ravaioli M, Nardo B, et al. Outcome of right hepatectomies in patients older than 70 years. Arch Surg. 2003;138:547–52.
25. Menon KV, Al-Mukhtar A, Aldouri A, Prasad RK, Lodge PA, Toogood GJ. Outcomes after major hepatectomy in elderly patients. J Am Coll Surg. 2006;203:677–83.
26. Shirabe K, Kajiyama K, Harimoto N, Gion T, Tsujita E, Abe T, et al. Early outcome following hepatic resection in patients older than 80 years of age. World J Surg. 2009;33:1927–32.
27. Reddy SK, Barbas AS, Turley RS, Gamblin TC, Geller DA, Marsh JW, et al. Major liver resection in elderly patients: a multi-institutional analysis. J Am Coll Surg. 2011;212:787–95.
28. Melloul E, Halkic N, Raptis DA, Tempia A, Demartines N. Right hepatectomy in patients over 70 years of age: an analysis of liver function and outcome. World J Surg. 2012;36:2161–70.
29. Yeh CN, Lee WC, Jeng LB, Chen MF. Hepatic resection for hepatocellular carcinoma in elderly patients. Hepatogastroenterology. 2004;51:219–23.

30. Su CW, Lei HJ, Chau GY, Hung HH, Wu JC, Hsia CY, et al. The effect of age on the long-term prognosis of patients with hepatocellular carcinoma after resection surgery: a propensity score matching analysis. Arch Surg. 2012;147:137–44.
31. Ettorre GM, Sommacale D, Farges O, Sauvanet A, Guevara O, Belghiti J. Postoperative liver function after elective right hepatectomy in elderly patients. Br J Surg. 2001;88:73–6.
32. Gruttadauria S, Doria C, Vitale CH, Cintorino D, Foglieni CS, Fung JJ, et al. Preliminary report on surgical technique in hepatic parenchymal transection for liver tumors in the elderly: a lesson learned from living-related liver transplantation. J Surg Oncol. 2004;88:229–33.
33. Yeh CN, Jan YY, Chen MF. Influence of age on surgical treatment of peripheral cholangiocarcinoma. Am J Surg. 2004;187:559–63.
34. Aldrighetti L, Arru M, Calori G, Caterini R, Comotti L, Torri G, et al. Impact of age on the outcome of liver resections. Am Surg. 2004;70:453–60.
35. Yeh CN, Jan YY, Chen MF. Hepatectomy for peripheral cholangiocarcinoma in elderly patients. Ann Surg Oncol. 2006;13:1553–9.
36. Caratozzolo E, Massani M, Recordare A, Bonariol L, Baldessin M, Bassi N. Liver resection in elderly: comparative study between younger and older than 70 years patients. Outcomes and implications for therapy. G Chir. 2007;28:419–24.
37. Wynne HA, Cope LH, Mutch E, Rawlins MD, Woodhouse KW, James OF. The effect of age upon liver volume and apparent liver blood flow in healthy man. Hepatology. 1989;9:297–301.
38. Frith J, Jones D, Newton JL. Chronic liver disease in an ageing population. Age Ageing. 2009;38:11–8.
39. Yoshimura Y, Kubo S, Shirata K, Hirohashi K, Tanaka H, Shuto T, et al. Risk factors for postoperative delirium after liver resection for hepatocellular carcinoma. World J Surg. 2004;28:982–6.