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REVIEW ARTICLE

The Use of Standardized Management Protocols for Critically Ill Patients with Non-traumatic Subarachnoid Hemorrhage: A Systematic Review

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Abstract

The use of standardized management protocols (SMPs) may improve patient outcomes for some critical care diseases. Whether SMPs improve outcomes after subarachnoid hemorrhage (SAH) is currently unknown. We aimed to study the effect of SMPs on 6-month mortality and neurologic outcomes following SAH. A systematic review of randomized control trials (RCTs) and observational studies was performed by searching multiple indexing databases from their inception through January 2019. Studies were limited to adult patients (age ≥ 18) with non-traumatic SAH reporting mortality, neurologic outcomes, delayed cerebral ischemia (DCI) and other important complications. Data on patient and SMP characteristics, outcomes and methodologic quality were extracted into a pre-piloted collection form. Methodologic quality of observational studies was assessed using the Newcastle–Ottawa scale, and RCT quality was reported as per the Cochrane risk of bias tool. A total of 11,260 studies were identified, of which 37 (34 full-length articles and 3 abstracts) met the criteria for inclusion. Two studies were RCTs and 35 were observational. SMPs were divided into four broad domains: management of acute SAH, early brain injury, DCI and general neurocritical care. The most common SMP design was control of DCI, with 22 studies assessing this domain of care. Overall, studies were of low quality; most described single-center case series with small patient sizes. Definitions of key terms and outcome reporting practices varied significantly between studies. DCI and neurologic outcomes in particular were defined inconsistently, leading to significant challenges in their interpretation. Given the substantial heterogeneity in reporting practices between studies, a meta-analysis for 6-month mortality and neurologic outcomes could not be performed, and the effect of SMPs on these measures thus remains inconclusive. Our systematic review highlights the need for large, rigorous RCTs to determine whether providing standardized, best-practice management through the use of a protocol impacts outcomes in critically ill patients with SAH.

Trial registration Registration number: CRD42017069173.

Keywords: Adult, Algorithm, Brain aneurysm, Clinical pathways, Critical care, Delayed cerebral ischemia, Neurocritical care, Standardized management protocols, Subarachnoid hemorrhage

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Introduction

Subarachnoid hemorrhage (SAH) is a devastating acute neurological condition with high overall morbidity and mortality. Despite advances in diagnostic and therapeutic capabilities, the 30-day mortality for SAH remains over 30% [1], and long-term outcomes are markedly impaired in up to one-half of survivors [2]. Affected patients have a mean age of 55 years [3], which is the youngest for any stroke sub-type and translates into a similar number of potential years of life lost compared to more common types of stroke [4]. Among survivors of SAH, up to 40% are unable to return to their previous occupations and 44–93% require some form of assistance with activities of daily living [2]. These lasting impairments contribute to the high economic burden of SAH and highlight its potentially under-recognized impacts to society.

High-quality treatments for patients with SAH are limited. Of the numerous interventions studied in large-scale clinical trials, only the use of enteral nimodipine [5], early aneurysm stabilization [6], rapid transfer to high-volume treatment centers [7] and greater use of endovascular services [8] have demonstrated a survival benefit, with varying levels of evidence. Data for other treatments are either equivocal or of low quality, leading to considerable uncertainty about the best approaches to manage patients [9]. This confusion was captured in a large multicenter survey of intensive care unit (ICU) physicians, which found that approaches in SAH management were often conflicting, outdated and heterogeneous [10]. Subsequently, the American Heart Association and Neurocritical Care Society (NCS) published a set of comprehensive policies partly to standardize the treatment of SAH [11, 12]. Additional efforts to standardize care have included the creation of dedicated endovascular neuroradiology fellowships and the requirement for comprehensive stroke treatment centers to possess certain elements deemed crucial for the proper care of patients with SAH [13].

Standardized management protocols (SMPs) have been studied as a tool to reduce heterogeneity in the care of complex patients. SMPs may improve the uptake of evidence-based guidelines, reduce cognitive load and facilitate communication among healthcare providers [14]. Protocol use has been linked to better outcomes for multiple hospitalized patient populations and contexts with varying levels of evidence [15–17]. Data on the role of SMPs in neurocritical care are more limited, with studies primarily examining their use in traumatic brain injury (TBI) patients [18, 19]. To date, no studies have systematically reviewed the use of SMPs in patients with SAH. SMPs for SAH management may improve consistency of care across large and small-volume centers; [7] reduce harmful heterogeneity in treatment approaches between care providers; [20] and standardize care across junior physicians and allied health staff, who may not be as comfortable making complex treatment decisions for this patient population. Given these and other potential benefits, we conducted a systematic review to determine whether the use of SMPs improves outcomes in critically ill patients with SAH. In addition, to better understand changing trends in SAH management, our secondary goal was to describe evolutions in the content, application and use of SMPs over time—highlighting what has changed and what has remained the same.

Methods

We performed this systematic review using a predefined protocol [21] according to current standards and adhering to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria [22]. Our protocol was registered with PROSPERO: International prospective register of systematic reviews (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42017069173).

Organizational Framework

Complications after SAH are typically encountered in distinct phases after the initial ictus. [23–25] We therefore developed a phase-based framework to select and organize SMPs, corresponding to the known main acute brain injury processes (see Supplemental Appendix 5). Within each group, protocols addressed specific aspects of care or complications which were most relevant to that particular disease-related phase:

1. Acute SAH: Protocols focused on early patient management, with an emphasis on rapid lesion stabilization and blood pressure control to prevent rebleeding (Time frame: Day 1).
2. Early brain injury (EBI): Protocols attempted to reduce high intracranial pressure (ICP) resulting from the initial hemorrhage and hydrocephalus (Time frame: Day 1–3).
3. Delayed cerebral ischemia (DCI): Protocols described strategies to prevent or minimize DCI using a combination of blood pressure management, inotropic support and/or angioplasty (Time frame: Days 3–14).

A further group was considered separately:

General neurocritical care: These protocols spanned the duration of the acute admission period and broadly addressed the critical care management of SAH patients.

To determine the effect of SMPs on SAH management, we analyzed studies that included a clearly defined

comparator arm. However, to fulfill our secondary goal of describing changing trends in SAH management, we chose *not* to exclude studies which lacked a control group. Such trends would potentially have been missed with a smaller sample size consisting of studies with only a control group. A quantitative synthesis was planned for the former group. Studies in the latter group were qualitatively analyzed to understand how our evolving knowledge of the pathophysiology of SAH has translated into changes in the content and use of SMPs. The quantitative and qualitative aspects of this systematic review were reported separately.

Search Strategy

We searched the following databases from inception to January 2019: MEDLINE, Embase, Cochrane Central, Web of Science and CINAHL. Our search strategy was composed of a combination of free-text keywords and medical subject headings terms (see Supplemental Appendix 1 for full search strategies). A search of the gray literature (Google Scholar, https://clinicaltrials.gov, and http://www.controlled-trials.com) was performed to identify relevant unpublished material. A hand search of published abstracts from The World Federation of Neurological Societies and the European Federation of Neurological Societies was also conducted as these journals are not indexed in EMBASE. Conference proceedings from all other neurologic journals relevant to this study are now available in EMBASE (Neurocritical Care Society, American Thoracic Society, European Society of Intensive Care Medicine, Society of Critical Care Medicine, Canadian Neurological Sciences Foundation, International Symposium of Intensive Care and Emergency Medicine) and were therefore not hand-searched. There were no language restrictions. We scanned the reference list of each included study to identify further potential material of interest.

Study Selection

We searched for studies of patients with non-traumatic SAH managed in an acute-care environment according to a standardized management protocol. Randomized control trials (RCTs), cohort studies (prospective or retrospective) and case series were selected if they reported the primary or secondary outcomes of interest. Selection was limited to those studies that included adult patients (age $\geq$ 18) with non-traumatic SAH (resulting from aneurysm rupture, dural arterio-venous fistula, arterial dissection or peri-mesencephalic lesion) who received protocol-guided management during their acute admission period. SMPs were defined as stepwise, organized pathways of care used to simplify medical decision making. To be considered an SMP, the study must have outlined a sequence of interventions and the specific conditions under which they were (or were not) implemented. Studies assessing individual treatments or the effect of a specific intervention were not considered SMPs. In addition, SMPs were considered distinct from "care bundles" in that the former are implemented in stepwise sequence, whereas the latter typically include groups of interventions implemented collectively [26]. Studies describing care bundles were not included. SMPs were classified as descriptive if they presented recommendations in general text without the aid of a graphic, schema or flowchart; or schematic if a graphical aid was used to guide decision making.

Study Screening and Data Abstraction

Citations were initially reviewed by title, keywords and abstract by one reviewer (ST). Articles passing the initial screen were subsequently reviewed in full by two reviewers (ST, VT). Two reviewers (ST, VT) independently retrieved data and methodological characteristics from the included studies using a standardized data collection form. This form (available in Supplemental Appendix 2) was pre-piloted on four studies and modified accordingly to ensure robustness. In cases of ambiguity or missing information, we contacted authors of the studies in question to clarify necessary details (see Supplemental Appendix 4 for the full list of authors contacted). Duplicate studies were included only once in the final analysis, with the most comprehensive article being chosen. We collected information on study design, baseline patient characteristics, mechanism of SAH, aneurysm management strategy (surgical clipping or endovascular coiling), characteristics of the SMP and rates of clinician adherence to the protocol. We resolved differences in extracted data between the two primary reviewers (ST, VT) by consensus or in consultation with a third reviewer (VAM). Data abstraction was performed for all studies, including those without a control arm.

Outcomes

Primary and secondary outcomes were compared for studies including a control group. Our primary outcome was long-term mortality at 6 months or greater following SAH. Our secondary outcomes included short-term mortality, defined as death within 21 days; length of stay in ICU and hospital; duration of mechanical ventilation; and neurologic outcomes. For the assessment of neurologic outcomes, we accepted studies that used the Glasgow Outcome Scale, extended Glasgow Outcome Scale (GOSe), modified Rankin Scale, Functional Independence Measure or the Disability Rating Scale. Many study authors reported neurologic outcomes according to their

own institutional standards. We considered these non-standardized grading scales as long as their parameters were consistent with other accepted measures of severity. Finally, as we expected variability in the choice of outcome reporting periods, we accepted a broad range of follow-up durations.

We also examined rates of adverse events and complications, including aneurysm rebleed, pneumonia, central nervous system infection, seizure occurrence, raised ICP, persistent hydrocephalus and DCI. Our analysis of DCI outcomes presented a unique challenge. Historically, the term 'vasospasm' was used to describe both radiological arterial vasoconstriction and the clinical entity of cerebral ischemia. However, according to updated definitions, the presence of radiographic arterial vasospasm is no longer required to make the diagnosis of DCI. For this review, we adapted a comprehensive definition of DCI from a widely cited consensus statement published by Vergouwen et al. in 2010 [27]. Studies assessing DCI were selected if they incorporated elements of the above definition, although given the large number of studies pre-dating this definition, few studies met all aspects of the consensus standard due to their use of older terminology. Thus, our adherence to the Vergouwen definition was close but not absolute.

Methodologic Quality and Risk of Bias Assessment

Two reviewers (ST, VT) independently assessed the quality of each cohort study (including those lacking a control arm) according to a modified version of the Newcastle–Ottawa Scale (NOS) [28]. The NOS is a validated eight-item checklist that assesses the quality of non-randomised studies. A star-system approach to grading allows for easy assessment of the variables of interest, and the aggregate score enables rapid recognition of the study's overall quality. We modified the NOS to include the most important SAH prognostic variables (see Supplemental Appendix 3 for our modified NOS). Two RCTs were included in this review, and their risk of bias was assessed with the Cochrane Collaboration's risk of bias tool [29].

Assessment of Quality of Evidence

As described in our protocol, we intended to use The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework to assess the quality of evidence for each reported outcome. Following the methods outlined in the Cochrane Handbook [29], we planned to summarize the quality of evidence as high, moderate, low or very low. However, after reviewing the included studies in detail, we determined that their overall quality was too low to permit a useful presentation of GRADE recommendations. We therefore excluded this step in our final report.

Data Analysis

A pre-piloted extraction form was used to collect data from each study. Categorical data were reported in proportions, while continuous data were presented as means with standard deviations or medians with ranges depending on the format used in the primary studies. As described in our study protocol, we planned to assess clinical heterogeneity by examining study populations, interventions and comparators; statistical heterogeneity would have been assessed for each outcome using the I2 statistic [21]. However, given important differences in outcome measures and insufficient data to permit pooling, we presented study results as a narrative summary.

Results

Literature Search

Our search strategy identified 11,250 studies. Of these, 34 full-length articles and three abstracts met our inclusion criteria, yielding the total of 37 studies (Fig. 1 and Table 1). Thirty-five studies were observational in nature and two were RCTs. All were published in English. Twelve studies originated from European centers and 17 were from North America. The year of publication ranged from 1982 to 2017, with 11 studies published before the year 2000. Thirty-three studies were single-centered. Sample sizes varied from 10 patients in the smallest study [30] to 865 patients in the largest [31] (Table 1).

Study Characteristics

In 12 studies, a control group was included where a subset of patients received non-protocolized care [31–42]. In seven of these studies, the control group was made up of patients who received usual care prior to the implementation of an institution-wide SMP [31, 35–37, 39, 41, 42]. The remaining 25 studies utilized SMPs in the care of all patients and did not include a control group [30, 43–66]. All of the included studies enrolled patients with aneurysmal SAH; no other etiologies meeting the inclusion criteria were found.

Two single-center studies assessed the effect of cisternal irrigation and head motion to relieve vasospasm [33, 34]. Both were conducted by the same primary author but on different patient groups at the same institution. Because of key differences in the study designs and SMPs, both studies were included and assessed separately. One study applied a protocol to patients with brain hemorrhages of which SAH patients were a unique subgroup with extractable outcomes [45]. The remaining studies enrolled only patients with aneurysmal SAH. Three

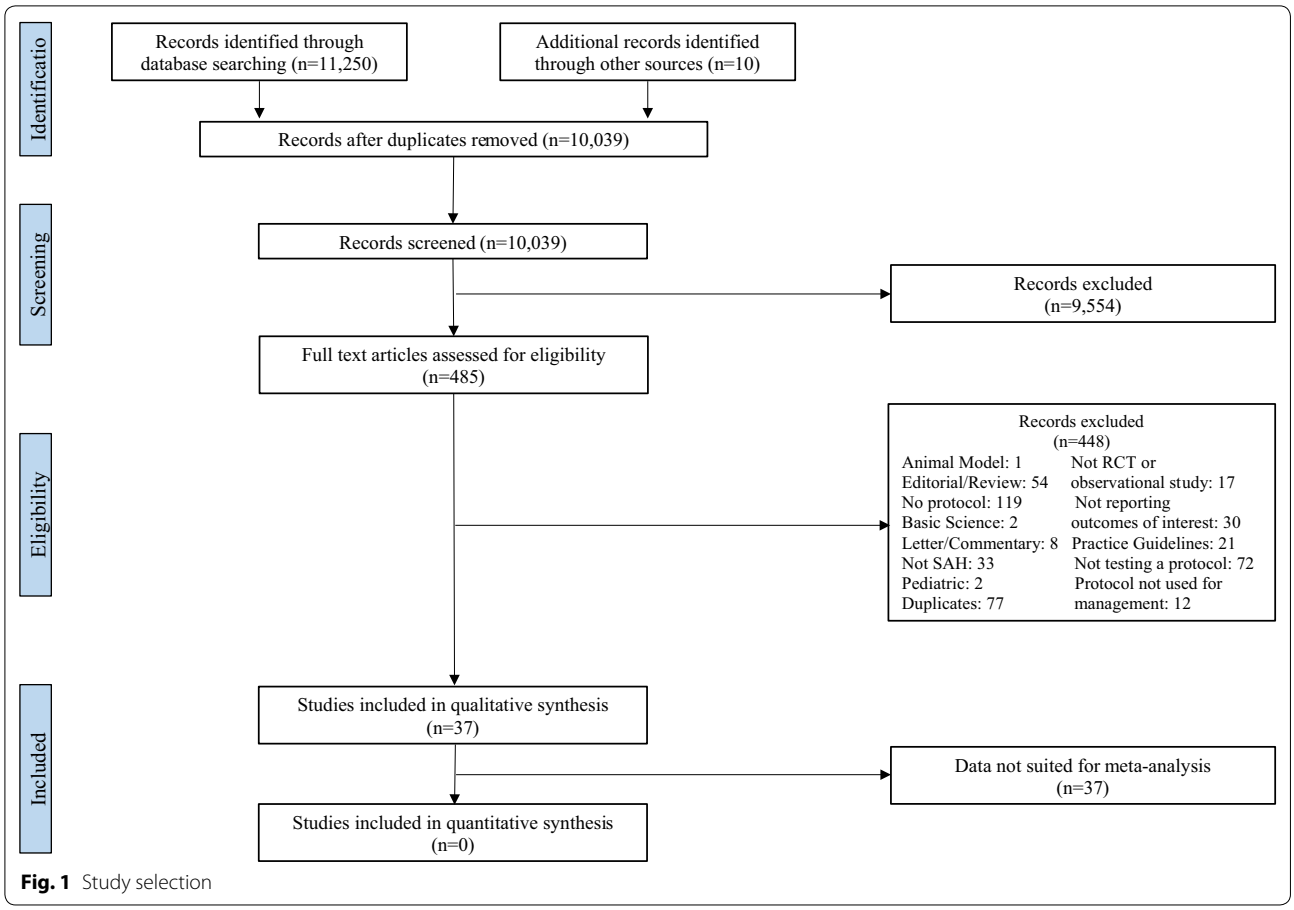

Fig. 1 Study selection

abstracts meeting our inclusion criteria were included in the final analysis, although we were unable to obtain additional data from their authors [38, 39, 58].

Patient and SMP Characteristics

Characteristics of the SMPs, organized by study design, are presented in Table 1. Components assessed by the SMPs are displayed in Fig. 2. Baseline characteristics are presented separately for studies with and without a control (Tables 2 and 3). The mean age of patients ranged from 45 to 60.8 years. Age did not differ significantly between the intervention and control groups. Men comprised between 17 and 75.6% of the study populations. Descriptive summaries of each SMP and additional details of management are presented in Supplemental Appendices 6 and 7.

Outcome Analysis in Studies with a Comparator

Primary Outcome

To determine whether protocol usage was associated with a change in mortality compared to usual care, studies including a control group were examined (see Table 4). Of the 12 studies with a control group, the primary outcome of mortality was assessed in six: one in-hospital [41], one at 3 months [42], one at discharge and 5–6 months [35] and one at 12 months [32]. In one of these studies, the primary outcome was aggregated across both treatment and control groups and not reported separately [36]. The final study was an abstract in which the reporting period for assessing mortality was not specified [39]. Only one study reported a statistically significant improvement in mortality in the protocol-managed group at 6 months ($p=0.04$) [35]. Given the clinical heterogeneity between the SMPs, a meta-analysis for mortality could not be performed.

Secondary Outcome

All studies with a control group examining secondary outcomes of interest are presented in Supplementary Appendix 9. Neurologic outcome was assessed in eight studies; two studies reported a statistically significant improvement in neurologic outcome with the use of an SMP [31, 34], four reported no difference between control and study groups [33, 36, 37, 40], and in two studies this information was unavailable [32, 42]. Outcomes were reported according to different neurologic scales,

Table 1 Characteristics of included studies

Author	Country	Study design	SMP group (N)	Control group (N)	Type of SMP	SMP description (intervention group)	Control group description	Primary outcomes	Secondary outcomes
Randomized controlled trials									
Eide et al. [32]	Norway	RCT	48	49	Flow diagram	ICP-directed care using mean wave amplitude	Non-mean wave amplitude-guided care	Mortality	RSS at 12 months
Hanggi et al. [33]	Germany	RCT	9	11	Descriptive protocol	Vasospasm management with lumbocisternal irrigation and head movement	Standard SAH management	N/A	mRS at discharge and 3 months. Physiologic/adverse events
Cohort studies									
Boonyawanakij et al. [43]	Thailand	Retrospective cohort	200	None	Flow diagram	ICP-directed care with lumbar drain	N/A	N/A	Postoperative GOS. Adverse events including DCI/vasospasm
Hanggi et al. [34]	Germany	Prospective cohort	20	20	Descriptive protocol	Vasospasm management with lumboventricular lavage and head rotation	Triple H therapy	N/A	mRS at 3 months, 6 months. Vasospasm rates
Kim et al. [35]	United States	Prospective cohort	279	174	Descriptive protocol	Hemodynamic management with a pulmonary artery catheter-guided fluid strategy	Fluid augmentation and vasopressors	Mortality at discharge and 6 months	Adverse events including DCI/vasospasm. Hospital length of stay
Latorre et al. [36]	United States	Retrospective cohort	166	166	Flow diagram	Aggressive hyperglycemia management with intravenous infusion protocol	Standard hyperglycemia management	Mortality	mRS at 3-6 month follow-up. ICU/Hospital LOS. Adverse events
Lerch et al. [37]	Switzerland	Retrospective cohort	198	150	Flow diagram	DCI management with triple H therapy, barbiturate coma, hypothermia and ICP control.	Non-neurointensivist-led care	N/A	GOS at 3 and 12 months. Adverse events including DCI/vasospasm
Manoel et al. [38]	Canada	Retrospective cohort	Not specified	20	Admission orders	General Neuro-ICU management	Historic control	N/A	Hospital and ICU length of stay

Table 1 (continued)

Author	Country	Study design	SMP group (N)	Control group (N)	Type of SMP	SMP description (intervention group)	Control group description	Primary outcomes	Secondary outcomes
Mejia-Matilla et al. [39]	Columbia	Retrospective cohort	24	26	Descriptive protocol	Hemodynamic management with continuous infusion of 5% albumin	Historic control (pre-albumin)	Mortality	Adverse events including DCI/vasospasm
Murphy et al. [40]	Canada	Retrospective cohort	13	12	Descriptive protocol	DCI management with induced hypertension/intra-arterial milrinone and angioplasty	Standard management with no induced hypertension	N/A	Neurologic outcomes at 3 months according to magnetic resonance spectroscopy
Naidech et al. [44]	United States	Prospective cohort	611	None	Descriptive protocol	Hemoglobin transfusion based on pre-set targets	N/A	N/A	mRS at 14 days and 3 months. Adverse events including vasospasm
Naidech et al. [45]	United States	Prospective cohort	122	None	Descriptive protocol	General Neuro-ICU management	N/A	N/A	Adverse events including DCI/vasospasm. ICU and hospital length of stay
Park et al. [31]	Korea	Retrospective cohort	442	423	Flow diagram	Emergency care protocol before aneurysm stabilization	Historic control without standardized care	N/A	mRS at 1 month. Adverse events
Suarez et al. [46]	United States	Prospective cohort	47	None	Descriptive protocol	Hemodynamic management with graded doses of albumin infusion	N/A	N/A	GOS, mRS, and Barthel Index at 3 months. Adverse events including DCI/vasospasm
Thiele et al. [41]	United States	Retrospective Cohort	343	491	Flow diagram	Management of hyperglycemia according to an IV insulin scale	Standard glucose management	In-hospital mortality	Adverse events including DCI/vasospasm
Whitfield et al. [42]	United Kingdom	Prospective/retrospective cohort	129	92	Flow diagram	Early surgical intervention and DCI management with triple H therapy	Non-protocolized fluid resuscitation	Mortality	GOS at 3 months. Adverse events. Hospital LOS

Table 1 (continued)

Author	Country	Study design	SMP group (N)	Control group (N)	Type of SMP	SMP description (intervention group)	Control group description	Primary outcomes	Secondary outcomes
Case series									
Armonda et al. [47]	United States	Case series	32	None	Flow diagram	Refractory DCI/Vasospasm management with pentobarbital coma and cerebral angioplasty (small component directed toward ICP control)	N/A	Mortality	Neurologic outcomes (not standardized) at 3 months. Adverse events
Awad et al. [48]	United States	Case series	118	None	Flow diagram	DCI management with hypervolemic hemodilution and arterial hypertension	N/A	Mortality *or* major neurologic deterioration	Adverse events including DCI/vasospasm
Bailes et al. [49]	United States	Case series	54	None	Flow diagram	ICP-directed care	N/A	Mortality at 3 months	Neurologic outcomes (not standardized). Adverse events including DCI/vasospasm
Barbarawi et al. (2009) [50]	Jordan	Case series	52	None	Descriptive protocol	DCI/vasospasm management with magnesium sulfate infusion	N/A	Mortality	Neurologic outcomes (not standardized). Adverse events including DCI/vasospasm
Boet et al. [51]	New Zealand	Case series	11	None	Descriptive protocol	DCI/vasospasm management	N/A	N/A	GOS at 3 mos. Adverse events including DCI/vasospasm
Corsten et al. [52]	United States	Case series	324	None	Descriptive protocol	Vasospasm/general neuro-ICU management including use of "HHH" therapy	N/A	Mortality at discharge and 6 month follow-up	Neurologic outcomes (not standardized)
Fandino et al. [53]	Switzerland	Case series	30	None	Descriptive protocol	DCI/vasospasm management with triple H therapy, papaverine infusion, angioplasty, and barbiturate coma	N/A	Mortality	GOS at 3 months. Adverse events including DCI/vasospasm

Table 1 (continued)

Author	Country	Study design	SMP group (N)	Control group (N)	Type of SMP	SMP description (intervention group)	Control group description	Primary outcomes	Secondary outcomes
Kassell et al. [54]	United States	Case series	58	None	Descriptive protocol	Vasospasm/DCI management from volume expansion and induced hypertension	N/A	N/A	Neurologic outcomes (non-standardized), adverse events
Kodama et al. [55]	Japan	Case series	212	None	Descriptive protocol	Vasospasm prevention with cisternal irrigation therapy	N/A	Mortality	Neurologic outcomes at discharge (non-standardized), adverse events
Lannes et al. [56]	Canada	Case series	88	None	Flow diagram	Symptomatic vasospasm management with milrinone infusion	N/A	Mortality	mRS at 1 and 12 months after SAH. Adverse events
Ljunggren et al. [57]	Sweden	Case series	60	None	Descriptive protocol	DCI management with early aneurysm operation and IV nimodipine	N/A	Mortality, functional outcomes on follow-up	Neurologic outcomes (non-standardized)
Martinez et al. [58]	Spain	Case series	65	None	Descriptive protocol	DCI/vasospasm management with endovascular approach after early surgery	N/A	Mortality	GOS at 3 months. Adverse events including DCI/vasospasm
Morgan et al. [59]	Australia	Case series	200	None	Descriptive protocol	DCI/vasospasm management with papaverine and angioplasty	N/A	Mortality	Neurologic outcomes (non-standardized). Adverse events including vasospasm. Healthcare costs
Mutoh et al. [60]	Japan	Case series	46	None	Descriptive protocol	Hemodynamic monitoring with thermodilution method	N/A	N/A	mRS at 1 month. Adverse events including DCI/vasospasm
Origitano et al. [61]	United States	Case series	43	None	Flow diagram	Vasospasm management with triple H therapy	N/A	Mortality	Neurologic outcomes (not standardized) at 3 months. Adverse events including DCI/vasospasm

Table 1 (continued)

Author	Country	Study design	SMP group (N)	Control group (N)	Type of SMP	SMP description (intervention group)	Control group description	Primary outcomes	Secondary outcomes
Seiler et al. [62]	Switzerland	Case series	153	None	Descriptive protocol	DCI management with early operation, IV nimodipine, and trans-cranial doppler	N/A	Mortality	GOS at 6 months. Adverse outcomes including DCI/vasospasm
Seule et al. [63]	Switzerland	Case series	100	None	Descriptive protocol	Vasospasm AND ICP management with therapeutic hypothermia	N/A	Mortality at 3 and 6 months.	GOS at 3 and 6 months. Adverse events
Solomon et al. [64]	United States	Case series	56	None	Descriptive protocol	General Neuro-ICU management including "HHH" therapy	N/A	Mortality	Neurologic outcomes (not standardized). Adverse events including DCI/vasospasm
Thomas et al. [30]	United States	Case series	10	None	Descriptive protocol	DCI management with sodium nitroprusside and thiosulfate	N/A	Mortality	mRS and GOS at 12-23 months. Adverse events including DCI/vasospasm
Vergouw et al. [65] *	Netherlands	Case Series	23	None	Flow diagram	Management of fluids and inotropes based on PiCCO monitoring	N/A	30-day mortality	Median daily GCS.
Yonekawa et al. [65]	Switzerland	Case series	150	None	Descriptive protocol	Intra-operative surgical management and DCI management with nimodipine, papaverine, and angioplasty	N/A	Mortality at discharge and 3 months	GOS at discharge and 3 months. Adverse events including DCI/vasospasm and surgical complications

DCI Delayed cerebral ischemia, *GCS* Glasgow coma scale, *GOS* Glasgow outcome scale, *ICP* Intracranial pressure, *ICU* Intensive care unit, *IV* Intravenous, *LOS* length of stay, *mRS* modified Rankin scale, *N/A* Not applicable, *PiCCO* Pulse contour cardiac output, *RCT* Randomized control trial, *RSS* Rankin stroke score, *SAH* Subarachnoid hemorrhage, *SMP* Standardized management protocol, *Triple H* Hypertensive hypervolemic hemodilution

*This study reported two separate but thematically linked studies, only one of which included patient management with an SMP. Each study within this publication assessed different outcomes. As a result, only data from the SMP-guided study were included. Moreover, since SMPs were applied to the first 23 eligible patients, the study was considered a case series

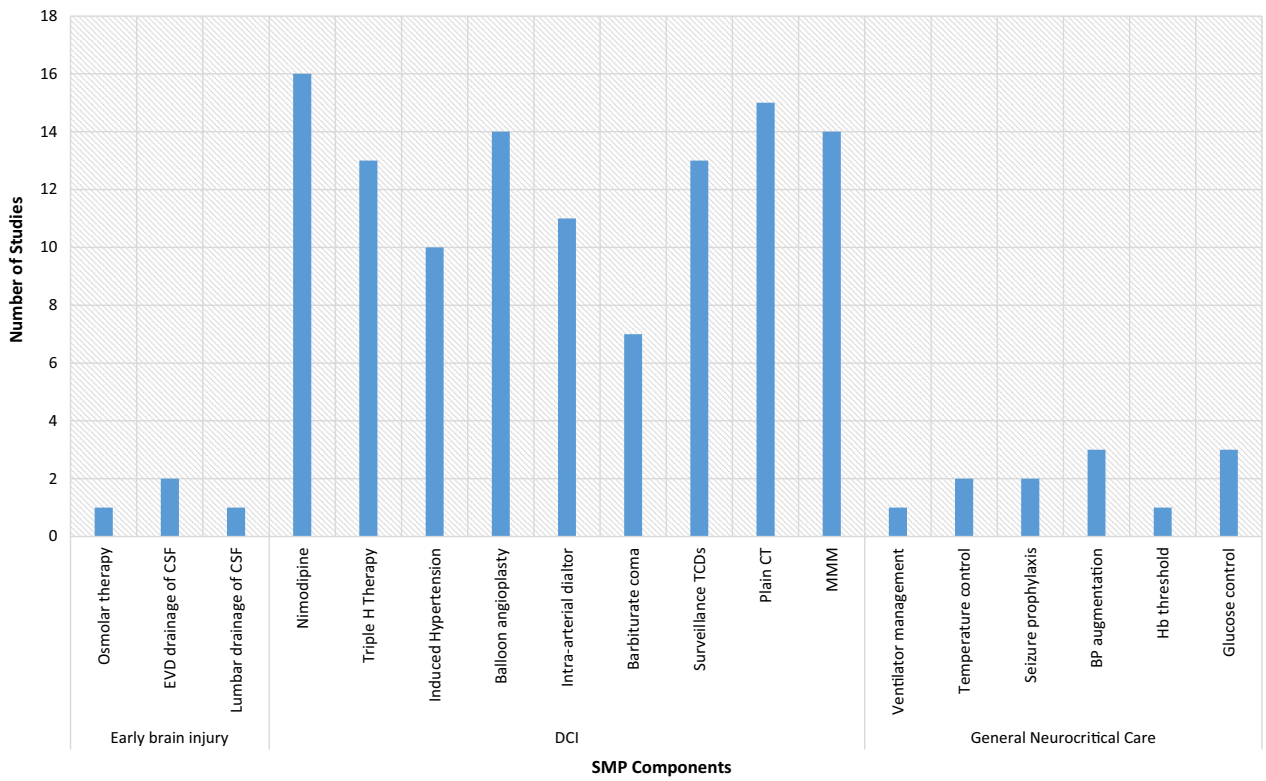

Fig. 2 Components assessed by the SMPs

and the timing of reported outcomes differed substantially, precluding meta-analysis. The following secondary outcomes were also assessed by one or more studies: ICU and hospital length of stay, delayed cerebral ischemia, aneurysm rebleed, pneumonia and hyponatremia, with significant heterogeneity. Given these limitations, the systematic review was extended to qualitatively review general themes of SMPs used to manage patients with SAH.

Outcome Analysis in Studies Without a Comparator

Qualitative Analysis

As described in our organizational framework, studies were categorized into four broad domains of care according to the time period of injury. Each of these domains is presented below, along with the studies fitting those domains.

Immediate Care After SAH

One study examined the effects of rapid protocolized endovascular coiling or surgical clipping [31] on patient outcomes. Patients with SAH were immediately considered for aneurysm stabilization and underwent either coiling or clipping with a mean duration of 2.9 and 3.1 h following admission, respectively.

Early Brain Injury

Four SMPs aimed to minimize EBI by targeting high ICP (one SMP in this group also focused on DCI management) [32, 43, 49, 63]. Strategies to achieve ICP targets included hypothermia, ventriculostomy placement with cerebrospinal fluid (CSF) evacuation and lumbar drainage. Intracranial hypertension management was also a minor component of three studies targeting DCI treatment, but since control of ICP was not their principle focus, these studies were categorized as DCI-driven [37, 47, 52].

Delayed Cerebral Ischemia

The most common protocol theme was management of DCI, with 22 studies using an SMP for this purpose. Thirteen studies focused on hypertension, hypervolemia and hemodilution (triple H) therapy to augment blood pressure. All of the studies using triple H were published between 1982 and 2009, whereas none published after 2009 incorporated this therapy. Depending on the SMP, triple H therapy was applied either as a prophylactic measure or in response to confirmed DCI. Blood pressure was augmented using intravenous fluids and/or inotropes, with targets often titrated to Swan-Ganz

Table 2 Patient baseline characteristics in studies with a control group

Study	Total (*n*)	Mean age years (SD)		Male sex *n* (%)		Poor Grade of SAH*		Aneurysm secured by Coiling *n* (%)	
		Cx	Tx	Cx	Tx	Cx	Tx	Cx	Tx
Eide et al. [32]	97	55.0 ± 13.0	56.0 ± 13.0	13 (26.5%)	15 (31.2%)	25 (51%)	21 (44%)	19 (38.8%)	22 (45.8%)
Hanggi et al. [33]	40	54.0 ± 11.4	57.3 ± 12.6	7 (35%)	6 (30%)	9 (45%)	15 (75%)	Coil: 10 (50%)	Coil: 0 (0%)
Hanggi et al. [34]	20	52.3 ± 15.1	60.8 ± 7.3	4 (36%)	5 (56%)	7 (64%)	6 (67%)	4 (36.4%)	4 (44.4%)
Kim et al. [35]	453	53.9	54.4	61 (35.3%)	80 (28.7%)	69 (39.7%)	96 (34.5%)	17 (9.8%)	29 (10.4%)
Latorre et al. 2009) [36]	332	54.9 ± 13.88	55.6 ± 13.07	44 (26.51%)	55 (33.10%)	65 (39.1%)	64 (38.5%)	32 (19.3%)	45 (27.1%)
Lerch et al. [37]	348	49.5 ± 12.5	52.2 ± 13.3	46 (30.7%)	54 (27.3%)	23 (15.3%)	93 (47%)	Coil: 0 (0%)	Coil: 0 (0%)
Manoel et al. [38]	N/A	N/A	N/A	N/A	N/A	Not reported	Not reported	Not reported	Not reported
Mejia-Matilla et al. [39]	50	57	58	5 (19.2%)	11 (45.8%)	Not reported	Not reported	Not reported	Not reported
Murphy et al. [40]	25	61.0 ± 12.1	58.2 ± 8.4	3 (25%)	4 (31%)	WFNS (median/ range): 1.9 ± 1.4	WFNS (median/ range): 2.6 ± 1.7	Not reported	Not reported
Park et al. [31]	865	55.5 ± 11.6	55.7 ± 12.9	125 (29.6%)	149 (33.7%)	69 (16.3%)	68 (15.4%)	92 (21.7%) None: 9 (2.1%)	167 (37.8%)
Thiele et al. [41]	834	N/A	N/A	109 (31.8%)	122 (24.8)	Not reported	Not reported	71 (20.7%)	189 (38.5%)
Whitfield et al. [42]	221	54	129	39 (42%)	52 (40%)	12 (13%)	16 (12.4%)	Not reported	Not reported

Cx Control, *HH* Hunt Hess, *N/A* Not applicable, *SD* Standard deviation, *SAH* Subarachnoid hemorrhage, *Tx* Treatment, *WFNS* World federation of neurosurgical surgeons

*Poor grade = HH ≥ 4 or WFNS ≥ 4

catheter outputs. Sixteen of the 22 DCI-based protocols incorporated use of the calcium channel blocker nimodipine to prevent or treat confirmed vasospasm. Sixteen studies also used invasive measures such as balloon angioplasty or catheter-directed papaverine infusion to manage refractory DCI secondary to cerebral vasospasm. Only one recent study described a detailed protocol for the use of milrinone to manage DCI [56]. Routine surveillance radiography was a specified component of 19 DCI-directed SMPs; this involved either trans-cranial Doppler, plain computerized tomography scan, cerebral angiogram or a combination of multiple modalities. Imaging practices (e.g., type of imaging, use of combination vs. individual modality and symptom-triggered vs pre-specified frequency) varied substantially according to institutional standards, with little similarity between studies.

Comprehensive/General Neurocritical Care

Six of the included studies addressed general neurocritical care approaches among patients with SAH. One presented in abstract forms the description of an admission order package [38]. Another described a comprehensive care strategy encompassing fluid management, mechanical ventilation strategies and blood pressure control [45]. The third described preoperative management and postoperative hemodynamic control [64]. The remaining three studies in this group described SMPs to address red blood cell transfusions [44] and glucose control [36, 41].

Methodological Quality

Methodologic quality of non-randomized studies varied widely, with studies scoring between 3 and 8 on the 9-point NOS (Table 5). Most studies lost points in the comparability and outcome categories, which reflected a failure to adjust the final outcome for either SAH severity or patient age, and lack of an appropriate length of follow-up. Risk of bias of the 2 RCTs is presented separately in Supplemental Appendix 8.

Discussion

In this systematic review, we sought to identify whether the use of SMPs improves patient outcomes after SAH. We additionally aimed to highlight changing trends in the use

Table 3 Patient baseline characteristics in studies without a control group

Study	Total (*n*)	Mean age (SD)	Male sex *n* (%)	Poor grade of SAH*	Aneurysm secured by Coiling *n* (%)
Armonda et al. [47]	32	47	7 (21.9%)	17 (53.1%)	17 (53.1%)
Awad et al. [48]	118	49	N/A	22 (19%)	0 (0%)
Bailes et al. [49]	54	55.7	21 (38.9%)	54 (100%)	Coil: 0 (0%) None: 19 (35.2%)
Barbarawi et al. [50]	52	45	28 (53.8%)	6 (11.5%)	31 (59.6%)
Boet et al. [51]	11 (10 completed the study)	53.9 ± 10.3	2 (20%)	1 (10%)	1 (10%)
Boonyawanakij et al. [43]	200	56	86 (43%)	68 (34%)	0 (0%)
Corsten et al. [52]	324	N/A	245 (75.6%)	79 (24.4%)	139 (43%)
Fandino et al. [53]	30	51 ± 8	11 (37%)	6 (20%)	0 (0%)
Kassell et al. [54]	58	51	17 (29.3%)	N/A	N/A
Kodama et al. [55]	217	59	90 (41.4%)	36 (16.6%)	0 (0%)
Lannes et al. [56]	88	53.4 ± 11.45	19 (21.6%)	22 (25%)	N/A
Ljunggren et al. [57]	60	45	28 (46.7%)	4 (6.7%)	0 (0%)
Martinez et al. [58]	65	56 ± 12	31 (47.7%)	N.A	26 (60.5%)
Morgan et al. [59]	200	N/A	N/A	N/A	0 (0%)
Mutoh et al. [60]	46	N/A	14 (30.4%)	23 (50%)	15 (32.6%)
Naidech et al. [44]	611	53.5 ± 14.3	197 (32.2%)	166 (27%)	N/A
Naidech et al. [45]	122	54.7 ± 13.7	41 (33.6%)	N/A	N/A
Origitano et al. [61]	43	46	15 (34.9%)	5 (11.6%)	0 (0%)
Seiler et al. [62]	153	52	49 (32%)	47 (30.7%)	0 (0%)
Seule et al. [63]	100	49.0 ± 12.6	36 (36%)	64 (64%)	4 (4%)
Solomon et al. [64]	56	N/A	N/A	2 (3.6%)	Coil: 0 (0%)
Suarez et al. [46]	47	51	13 (27.6%)	0 (0%)	34 (72.3%)
Thomas et al. [30]	10	52.3 ± 10.1	4 (40%)	2 (20%)	2 (20%)
Vergouw et al. [65]	23	55 ± 3.4	4 (17%)	N/A	9 (39%)
Yonekawa et al. [65]	150	49.5	46 (30.7%)	23 (15.3%)	0 (0%)

HH Hunt Hess, *N/A* Not applicable, *SAH* Subarachnoid hemorrhage, *SD* Standard deviation, *WFNS* World Federation of Neurological Societies

*Poor grade = HH ≥ 4 or WFNS ≥ 4

of SMPs for SAH management. Due to clinical and methodological heterogeneity, a meta-analysis of studies could not be performed, and therefore the effect of SMPs on 6-month mortality or neurologic outcomes remains inconclusive. From a qualitative perspective, we found that SMPs are regularly used to manage patients with SAH. Few protocols addressed the full spectrum of ICU-level care that patients with SAH typically require, perhaps reflecting the reality that no single protocol can capture every step in the management of this complex and dynamic condition. Finally, changing trends in SAH management were most readily apparent in fluid management strategies and the treatment of DCI. Whereas triple H therapy was a common element of protocols published before 2009, this intervention was not a feature of more contemporary SMPs—consistent with recent concerns regarding fluid overuse to prevent or treat ischemic complications of SAH.

Our study highlights several crucial gaps in the current use of protocols to standardize the management of patients with SAH. First, the majority of studies included in our review describe small, single-center interventions with significant clinical heterogeneity between institutional protocols. In interventional clinical trials, between-center differences may affect the estimated treatment effect and create significant challenges for the design, conduct and interpretation of future research. Second, few institutions systematically track rates of adherence to SMPs—in our systematic review, only one study reported this variable [38]. This could mean that important differences between SMP and control groups are masked by lack of adherence to the SMP. Finally, there is little consistency among studies in the definition and reporting of DCI [67]. Neurologic deterioration due to various factors (e.g., seizure, metabolic derangement) could be inappropriately attributed to DCI in the absence of true DCI. Moreover, multiple mechanisms may simultaneously account for a patient's neurologic deterioration. Thus, DCI could be under- or over-called based on differences

Table 4 Primary outcome analysis in studies with a control group

Author	Study design	SMP group (N)	Control group (N)	Type of SMP	SMP description (intervention group)	Control group description	Follow-up period	Primary outcome analysis
Eide et al. [32]	RCT	48	49	Flow diagram	ICP-directed care using mean wave amplitude	Non-mean wave amplitude-guided care	Mortality at 12 months	Study Group: 7 (14.6%) Control Group: 9 (18.4%)
Kim et al. [35]	Prospective cohort	279	174	Descriptive protocol	Hemodynamic management with a pulmonary artery catheter-guided fluid strategy	Fluid augmentation and vasopressors	Mortality at discharge and 6 months	Study Group at discharge: 73 (26%) Control Group at discharge: 48 (28%) p = 0.334 Study Group at 6 mos: 80 (29%) Control Group at 6 mos: 59 (34%) p = 0.04
Latorre et al. [36]	Retrospective cohort	166	166	Flow diagram	Aggressive hyperglycemia management with intravenous infusion protocol	Standard hyperglycemia management	Mortality (follow-up not specified)	Data not separated by groups
Mejia-Matilla et al. [39]	Retrospective cohort	24	26	Descriptive protocol	Hemodynamic management with continuous infusion of 5% albumin	Historic control (pre-albumin)	Mortality (follow-up not specified)	Study Group Mortality: 6 (25%) Control Group Mortality: 7 (26.9%)
Thiele et al. [41]	Retrospective cohort	343	491	Flow diagram	Management of hyperglycemia according to an IV insulin scale	Standard glucose management	In-hospital mortality	Study Group: 59 (12.0%) Control Group: 40 (11.7%)
Whitfield et al. [42]	Prospective/retrospective cohort	129	92	Flow diagram	Early surgical intervention and DCI management with triple H therapy.	Non-protocolized fluid resuscitation	Mortality at 3 months	Study Group: 22 (17.1%) Control Group: 18 (19.6%)

DCI Delayed cerebral ischemia, *ICP* Intracranial pressure, *IV* Intravenous, *RCT* Randomized control trial, *SMP* Standardized management protocol, *Triple H* Hypertensive hypervolemic hemodilution

in clinical context and definitions, rendering the results of an intervention (e.g., the use of an SMP) challenging to interpret.

Our study also highlights important avenues for future research in the management of SAH. For example, the large number of DCI-based studies in the literature suggests that DCI is an attractive and feasible condition to treat with SMPs. DCI remains a significant cause of morbidity and mortality following SAH. High-quality SMPs may enable clinicians to follow a stepwise approach to the treatment of DCI, covering various aspects of management (e.g., when to obtain imaging, how to treat and when to consider invasive measures) which are not always clear. Furthermore, there remains a need to harmonize disparate definitions of key outcome measures after SAH, of which DCI and neurologic disability are just two examples. The recently launched Common Data Elements (CDE) initiative partly addresses this problem by standardizing definitions, naming and data collection for studies in major neurologic disorders [68]. In particular, the care of patients with SAH has been a specific focus of the CDE initiative, with multiple studies advocating for the standardization of patient management [69–72]. Such standardization would enable meaningful comparisons between studies conducted at different hospitals and testing different interventions. Significant differences in SAH management across

Table 5 Methodologic quality assessment of observational studies

Study	Selection/4	Comparability/2	Outcome/3	Total/9
Armonda et al. [47]	3	0	1	4
Awad et al. [48]	2	0	1	3
Bailes et al. [49]	4	1	2	7
Barbarawi et al. [50]	3	0	2	5
Boet et al. [51]	3	0	1	4
Boonyawanakij et al. [43]	4	1	3	8
Corsten et al. [52]	4	1	3	8
Fandino et al. [53]	3	0	2	5
Hanggi et al. [34]	4	2	2	8
Kassell et al. [54]	3	0	1	4
Kim et al. [35]	4	2	2	8
Kodama et al. [55]	4	2	2	8
Lannes et al. [56]	4	2	2	8
Latorre et al. [36]	4	2	2	8
Lerch et al. [37]	3	1	2	6
Ljunggren et al. [57]	3	2	2	7
Manoel et al. [38]	Insufficient information			
Martinez et al. [58]	Insufficient information			
Mejia-Matilla et al. [39]	Insufficient information			
Morgan et al. [59]	3	0	2	5
Murphy et al. [40]	4	1	3	8
Mutoh et al. [60]	4	1	2	7
Naidech et al. [44]	4	2	2	8
Naidech et al. [45]	3	1	2	6
Origitano et al. [61]	3	0	2	5
Park et al. [31]	4	2	2	8
Seiler et al. [62]	3	2	3	8
Seule et al. [63]	3	0	2	5
Solomon et al. [64]	3	1	3	7
Suarez et al. [46]	4	1	2	7
Thiele et al. [41]	3	0	2	5
Thomas et al. [30]	3	1	3	7
Whitfield et al. [42]	4	2	2	8
Vergouw et al. [65]	4	1	2	7
Yonekawa et al. [65]	4	1	2	7

hospitals might also provide an opportunity to better understand the impact of care practices using comparative effectiveness research methods [73].

Although the efficacy of SMPs in patients with SAH remains inconclusive, protocols have been shown to improve outcomes after other severe neurologic injuries. In a systematic review by English et al., protocol use was associated with reduced morbidity and mortality at 6 months in patients with TBI [18]. A recent large North American-based study by McCredie et al. evaluating the outcome of ICU structure and processes of care in patients with severe TBI found that SMPs were associated with lower in-hospital mortality [19]. However, a similar level of support has not been demonstrated for SMP use in patients with SAH. This may be related in part to the weak overall evidence base to guide management policies. As a case in point, the 2011 NCS consensus recommendations highlighted that existing data on SAH management are of low-to-moderate overall quality [11]. SMPs may offer the possibility of improving the treatment of SAH by aggregating the highest quality literature into a template which enables uniform, best-practice management.

The strengths of this systematic review lie in its a priori design, broadly inclusive search strategy and methodologic rigor. As per best practices [22], this review was registered on PROSPERO and followed a pre-specified protocol [21] for methodology and analysis. For all steps done in duplicate, reviewers were blinded to each other's assessment. We additionally summarized the quality of all existing literature in this domain using a validated quality assessment metric.

Our study has important limitations. As described, a major challenge was the lack of consistency in defining DCI. Despite our best effort to include only those studies which defined DCI comprehensively [27], it is possible that we were either too liberal or restrictive in our selection. We were additionally challenged by variability in the reporting of neurologic outcomes. Although we decided a priori to include such studies if their parameters aligned with commonly used scales, this was often challenging due to lack of clear or comprehensive reporting. Finally, our review was limited to common patient-level outcomes. SMPs may have important effects on other outcomes, such as physician convenience, reduced phlebotomy for testing, improved communication between the healthcare team and reduction in cognitive load. These were not formally assessed in our systematic review.

Conclusions

The efficacy of SMPs to improve 6-month mortality in patients with SAH remains inconclusive. The available literature is composed primarily of small-scale, single-center studies of variable quality, with heterogeneous definitions of key outcomes and lack of harmonization across institutional SMPs. Given the large number of low-quality studies published in this research area, our systematic review highlights the need for large, rigorous, RCTs to determine whether providing standardized, best-practice management through the use of SMPs impacts patient-centered outcomes in critically ill adults with SAH.

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Authors Contributions
ST participated in study planning, data screening, acquisition, and analysis, appraising the quality of studies, manuscript preparation and proofreading, and critical revisions. VT participated in data screening, acquisition, and analysis, and manuscript proofreading. JMS participated in study planning and manuscript proofreading. SWE participated in study planning and manuscript proofreading. VAM participated in study planning, developing the search strategy, manuscript preparation and proofreading, and critical revisions.

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The authors declare that they have no conflict of interest.

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