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Simon, G., Craswell, A., Thom, O., & Fung, Y. L. (2017). Outcomes of restrictive versus liberal transfusion strategies in older adults from nine randomised controlled trials: a systematic review and meta-analysis. Lancet Haematology, 4(10), e465–e474. https://doi.org/10.1016/S2352-3026(17)30141-2
Document Type: Accepted Version

Link to Published Version: https://doi.org/10.1016/S2352-3026(17)30141-2

Original article published online (www.thelancet.com/haematology) September 11, 2017
http://dx.doi.org/10.1016/S2352-3026(17)30141-2

Outcomes of restrictive versus liberal transfusion strategies in older adults from nine randomised controlled trials: a systematic review and meta-analysis

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Summary

Background Guidelines for patient blood management recommend restrictive transfusion practice for most adult patients. These guidelines are supported by evidence from randomised controlled trials (RCTs); however, one of the patient groups not explicitly examined in these studies is the geriatric population. We examined RCTs relevant to transfusion outcomes in older patients. Our aim was to determine whether special guidelines are warranted for geriatric patients, recognising the different pathophysiological characteristics of this group.

Methods For this systematic review and meta-analysis, we searched PubMed, Scopus, and the Cochrane Library databases from their inception to May 5, 2017, for evidence relating to transfusion outcomes in adults aged 65 years and older. This criterion was widened to include RCTs where a substantial proportion of the study population was older than 65 years. We also included study populations of all clinical settings, and did not limit the search by date, language, or study type. For articles not in English, only available translations of the abstracts were reviewed. Studies were excluded if they did not specify age. Observational studies and duplicate patient and outcome data from studies that generated multiple publications were also excluded. We screened bibliographies of retrieved articles for additional publications. We analysed data extracted from published RCTs comparing restrictive and liberal transfusion strategies in older adults. We generated fixed effects risk ratios (RR) for pooled study data using the Mantel-Haenszel method. Primary outcomes were 30-day and 90-day mortality events for patients enrolled in restrictive and liberal transfusion study groups. We included intention-to-treat outcome data in the meta-analysis when available, otherwise we used per-protocol outcome data.

Findings 686 articles were identified by the search, and a further 37 by the snowball approach. Of these articles, 13 eligible papers described findings from nine RCTs (five trials investigating orthopaedic surgery, three cardiac surgery, and one oncology surgery; including 5780 patients). The risk of 30-day mortality was higher in older patients who followed a restrictive transfusion strategy than in those who followed a liberal transfusion strategy (risk ratio [RR] 1·36, 95% CI 1·05–1·74; p=0·017). The risk of 90-day mortality was also higher in those who followed a restrictive transfusion strategy than in those who followed a liberal transfusion strategy (RR 1·45, 95% CI 1·05–1·98; p=0·022).

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Original article published online (www.thelancet.com/haematology) September 11, 2017
http://dx.doi.org/10.1016/S2352-3026(17)30141-2

Interpretation Liberal transfusion strategies might produce better outcomes in geriatric patients than restrictive transfusion strategies. This outcome contradicts current restrictive transfusion approaches. Population ageing will challenge resources globally, and this finding has implications for blood supply and demand, and optimal care of older adults. Further research is needed to formulate evidence-based transfusion practice across clinical specialties specific to the geriatric population, and to examine resource effects.

Funding Australia's National Blood Authority.

Introduction

Currently, a range of blood transfusion guidelines developed by diverse organisations in different countries exists. Guidelines are supported by studies that have reported that restrictive transfusion strategies do not produce worse outcomes than liberal strategies, with restrictive transfusion conserving resources and minimising patient exposure to allogenic blood.[1–5] An accumulating body of evidence is based on randomised controlled trials (RCTs).[1] One of the patient groups not explicitly examined in most studies of transfusion strategies is the geriatric population.[6–8]

Consideration of general guidelines and individual patient condition is important in making transfusion decisions.[9] For geriatric patients, underlying comorbidities might alter their physiological reserve and their ability to respond to a range of stressors. Among the 15 diseases with the highest burden for the older adult population, those with implications for transfusion decision making include ischaemic heart disease, stroke, and chronic obstructive pulmonary disease.[10] It is unclear whether increasing age per se creates circumstances of increased risk associated with anaemia and transfusion.[11] The perceived frailty of a geriatric individual might be of greater importance than their chronological age when determining appropriate courses of treatment.[12]

Evidence regarding links between morbidity, mortality, and blood transfusion is conflicted. Some observational studies have reported worse outcomes associated with transfusion, such as increased mortality, cardiac complications, infection incidence, and length of hospital stay.[13,14] Several studies report no effect of transfusion on those outcomes, whereas some studies indicate reduced or increased numbers of complications and mortality associated with transfusion.[13,14]

Specific patient blood management guidelines have been developed to recognise the special needs of the paediatric population.[15,16] Patients aged 65 years and older (from now on referred to as older adults) use the greatest proportion of the blood supply.[17–19] Recognising the accumulation of comorbidities and changes in physiological function and capacity with age, we postulate that specific patient blood management guidance is warranted for this older population.

In this paper, we critically assessed the findings from several RCTs that had examined restrictive versus liberal transfusion strategies in older adults, as distinct from the patient population of younger adults. We present a meta- analysis of outcome data related to mortality, cardiac complications, myocardial infarction, infection incidence, and length of hospital stay.

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Research in context

Evidence before this study

Much effort has been directed towards development of patient blood management strategies and guidelines. There is now increased focus on assessment of individual risk and benefit during transfusion decision making. Paediatric guidelines have been published, recognising the special physiological needs of young patients. However, we did not identify any specific patient blood management guidelines for older patients.

We did a literature review and examined evidence from randomised controlled trials (RCTs) regarding transfusion outcomes for older patients. We searched PubMed, Scopus, and the Cochrane Library databases from their inception to May 5, 2017. The search was not limited by clinical setting, date, language, or study type. Articles not in English were excluded if translations of the abstracts were not available, and if studies did not specify age. Observational studies and duplicate patient and outcome data from studies that generated multiple publications were also excluded. Medical Subject Headings and free-text terms relating to the concepts of geriatric and transfusion were used. 13 papers relating to nine recent RCTs with a geriatric focus were identified. The studies examined orthopaedic, cardiac, and oncology surgery settings. Outcome data for 5780 patients from these RCTs were included in our meta-analysis and assessment of bias, following Cochrane and PRISMA methods.

Added value of this study

To our knowledge, this study is the first published meta-analysis of RCTs focused on geriatric-specific transfusion outcomes. Pooled RCT outcome data analysed in our study identify that liberal transfusion strategies had better geriatric patient outcomes with respect to 30-day and 90-day mortality and cardiovascular complications than restrictive transfusion strategies. Risk of myocardial infarction showed no difference; and risks of infections and length of hospital stay were equivalent between the transfusion groups. These findings bring into question the appropriateness of restrictive transfusion strategies for older patients. It highlights the need for geriatric-specific consideration in the development and revision of patient blood management guidelines, to bookend the paediatric guidelines that have been developed.

Implications of all the available evidence

There is a growing body of evidence from RCTs to address several conflicts in transfusion medicine. RCT evidence was identified that is specific to transfusion in older adults.

Meta-analysis of these RCTs indicates that liberal transfusion strategies might provide better outcomes for the geriatric patient groups included in the studies than restrictive transfusion strategies. Further geriatric-specific studies are needed to guide the development and revision of patient blood management and transfusion guidelines for older adults.

Methods

Search strategy and selection criteria

We did a systematic review following the PRISMA[20] guideline to assess the quality and quantity of peer-reviewed, geriatric-transfusion-specific evidence. Subsequently, we did a meta-analysis with the RCTs yielded from the search.

The research team developed and agreed on the search and screening protocols (appendix p 1) before the database searches were done. The initial inclusion criteria of the search strategy were study findings specific to patients aged 65 years or older, and study populations of all clinical settings. However, limiting the inclusion of articles to studies of patients aged 65 years and older yielded only three RCTs. Hence, this inclusion criterion was widened to include RCTs for which a substantial proportion of the study population was older than 65 years. Although some included studies had age recruitment criteria commencing at 16 years or 18 years, the mean age for all studies was at least 64 years. Additionally, the search strategy was not limited by date, language, or study type. For articles not in English, only available translations of the abstracts were reviewed. Studies were excluded if they did not specify age; additionally, observational studies were excluded. For studies that generated multiple publications (the transfusion requirements in frail elderly [TRIFE] study,[6,21–23] and functional outcomes in cardiovascular patients undergoing surgical hip fracture repair [FOCUS] trial[24,25]), we excluded duplicate patient and outcome data from the meta-analysis. No other patients or groups were excluded.

We identified RCTs by searching PubMed, Scopus, and the Cochrane Library database from their inception to May 5, 2017. Medical Subject Headings (MeSH) and free-text terms relating to the concepts of geriatric and transfusion were used: "("Health Services for the Aged" [MeSH] OR "Homes for the Aged" [MeSH] OR "Geriatric Assessment" [MeSH] OR "Geriatric Nursing" [MeSH]) AND ("Blood Transfusion" [MeSH] OR "Transfusion Reaction" [MeSH] OR "Transfusion Medicine" [MeSH] OR "Platelet Transfusion" [MeSH] OR "Erythrocyte Transfusion" [MeSH] OR "Blood Component Transfusion" [MeSH] OR "Blood Transfusion, Autologous" [MeSH])". We also did MeSH searches using subsets of these terms—ie, for geriatric we used "("Health Services for the Aged" [MeSH] OR "Homes for the Aged" [MeSH] OR "Geriatric Assessment" [MeSH] OR "Geriatric Nursing" [MeSH])" and for transfusion we used "("Blood Transfusion" [MeSH] OR "Transfusion Reaction" [MeSH] OR "Transfusion Medicine" [MeSH] OR "Platelet Transfusion" [MeSH] OR "Erythrocyte Transfusion" [MeSH] OR "Blood Component Transfusion" [MeSH] OR "Blood Transfusion, Autologous" [MeSH])".

We screened titles and retrieved abstracts with relevant titles. Abstracts were assessed against research topics related to transfusion and specific to older adults as described in the appendix (p 1). We used a snowball sampling approach to scan the citation lists of retrieved articles for additional articles relevant to the research topics and retrieved relevant titles.

GIS undertook the primary role for the searches and screening of articles against the predefined study protocol. Issues of inadequate clarity in the study protocols or retrieved citations were resolved with YLF, and referred to AC or OT when agreement was not reached.

Data analysis

We excluded non-relevant and duplicate citations and examined the remaining articles in full. Additionally, we used Review Manager (version 5.3)[26] to do a meta-analysis and derive forest plots, heterogeneity estimates, and for risk of bias assessments. Primary outcomes included in the meta-analysis were 30-day and 90-day mortality. Secondary outcomes were composite cardiac complications, myocardial infarction, composite infection incidence, and

length of hospital stay.

For studies that reported intention-to-treat and per- protocol outcome data, we included the intention-to-treat data in our meta-analysis. We used the Mantel-Haenszel method[27] using a fixed effects model for meta-analysis of dichotomous data. For continuous data, we used the inverse variance method using a fixed effects model. We extracted raw data for patient and event numbers from publications for analysis. We used risk ratios (RRs) for dichotomous data elements and mean differences for continuous data to align with other recent publications on transfusion strategies.[1,28,29] When composite and specific cardiac outcomes were reported, only composite outcomes were included in meta-analysis. For papers without composite cardiac outcomes, we used myocardial infarction as a cardiac outcome and pooled it separately in the meta-analysis. Some studies reported length of hospital stay outcomes using mean (SD), whereas others reported median (IQR). For our meta-analysis, median values were equated to means, and IQR values were converted to SDs as described in the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0).[30] Broadening the study inclusion criteria to incorporate studies with some younger patients introduced heterogeneity with respect to age. Therefore, we did a sensitivity analysis for each of the study outcomes, through subgroup analysis of the three RCTs that only recruited patients aged 65 years and older.

We assessed study bias by comparing published study protocols and methods against the criteria for judging risk of bias outlined in the Cochrane Handbook.[31] Subsequently, we evaluated risk of bias at the study level on the basis of information in each publication and did not contact study authors. The appendix (pp 2–3) summarises the assessment of the bias of individual studies and overall bias. I^2 was used as an indication of study heterogeneity.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of 686 articles screened, 98 were reviewed in full (figure 1). 625 articles were excluded because the study population was not specific to geriatrics and transfusion. 13 papers described findings from nine RCTs, because two studies were represented by more than one paper each. The findings of the RCTs were published between 2009 and 2016, with eight (62%) of 13 papers published in 2015–16.

Nine geriatric-transfusion-related RCTs,[6,21–25,32–38] representing 5780 patients (2887 restrictive strategy and 2893 liberal strategy), were identified for inclusion in this meta-analysis (table 1). Only three RCTs,[6,32,33] representing 590 patients (298 restrictive and 292 liberal strategies), were restricted to patients aged 65 years and older. Eight (89%) of nine studies reported patient cohort ages using mean and SD, whereas one[38] (11%) reported median and IQR. The appendix (pp 5–7) outlines study aims and outcomes, and an overview of transfusion rates and quantities.

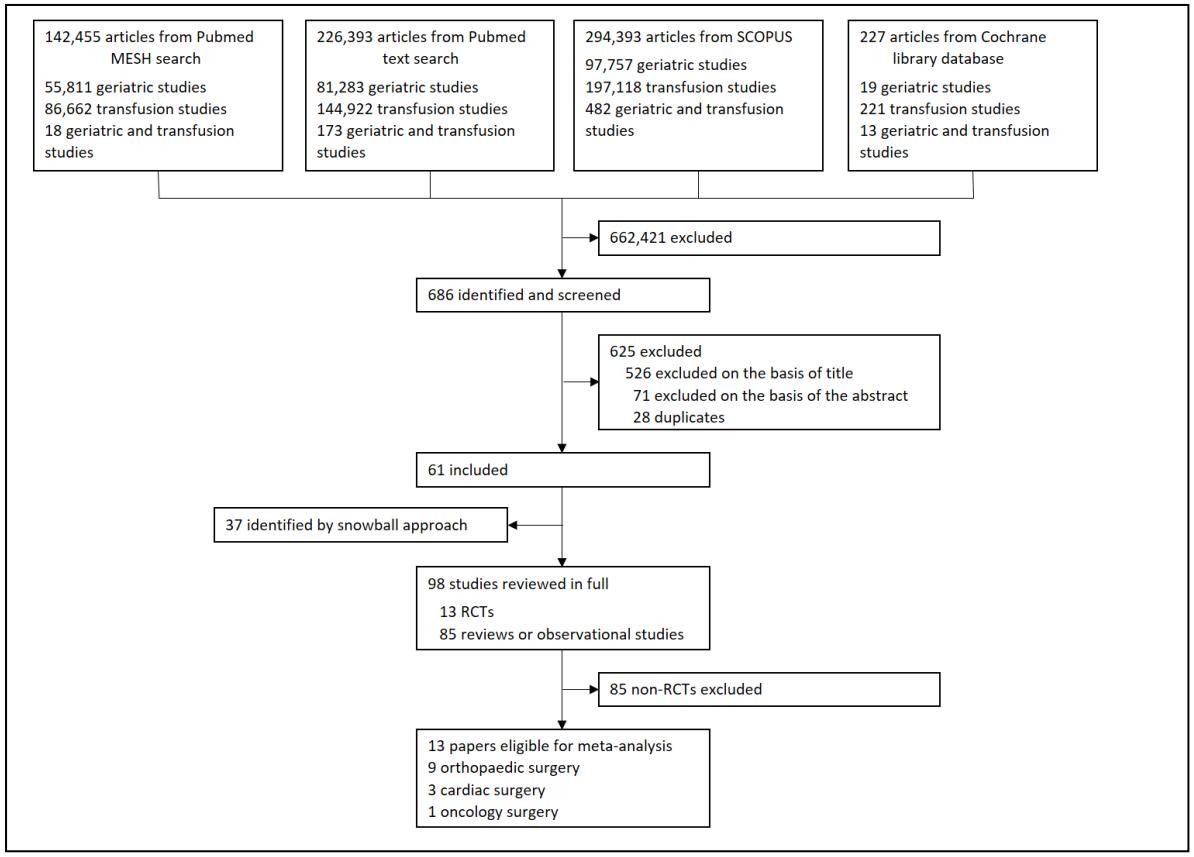

Figure 1: study selection profile
Numbers of geriatric and transfusion-focused studies were excluded from the total number of articles for each database search to avoid duplicative counting, as these articles were common to both search terms. MeSH=Medical Subject Headings. RCTs=randomised controlled trials.*Articles excluded were not geriatric and transfusion focused. †Reviews or studies of anaemia, physiology of ageing, or transfusion. ‡Of the nine orthopaedic surgery papers included for meta-analysis, there were five distinct RCTs because two studies generated multiple publications (TRIFE study[6,21–23] and FOCUS trial[24,25]).

The major sources of bias identified were inadequate masking of treating clinicians to the randomised transfusion strategy, and some reported outcomes were not specified as primary or secondary outcomes in the RCTs. The appendix (pp 2,3) provides further discussion of study bias and a summary and graph of the risk of bias. Although the paucity of studies (nine studies for mortality, eight each for cardiac and infection, and six for length of stay) precluded analysis of funnel plots, they have been included in the appendix (pp 3–5).[39]

Table 2 summarises our meta-analysis' findings for the studies' primary and secondary outcomes. Mortality outcomes were reported by eight papers, at time intervals ranging from 10-day to 3-year endpoints (appendix p 6). The most common outcome endpoints were at 30 days (seven [88%] of eight studies) and 90 days (two [25%] of eight); hence, these endpoints were included for meta- analysis. Older patients who followed a liberal transfusion strategy had a significantly lower risk of 30-day mortality than did those who followed a restrictive transfusion strategy (RR 1·36, 95% CI 1·05–1·74; p=0·017). A similar result was seen in the meta-analysis of the two studies that reported 90-day mortality outcomes (1·45, 1·05–1·98; p=0·022; figure 2).

	Study name	Country of study	Study size	Characteristics of cohort	Hb thresholds for restrictive vs liberal transfusions (g/L)	Study age cut-off (years)	Age of cohort (years)		Proportion of women in cohort			
							Restrictive	Liberal	Restrictive n/N %		Liberal n/N %	
Studies restricted to patients aged ≥ 65 years												
Gregersen (2015, 2016)[6,28,29]	TRIFE	Denmark	284	Patients who had had hip surgery and were residents of nursing homes and sheltered housing	97 v 113	≥ 65	85·7 (SD 6·9)	86·9 ± 9·8†	108/ 144	75%	106/ 140	76%
Blandfort (2016)[27]	Subgroup of TRIFE	Denmark	179	Patients who had had hip surgery and were residents of nursing homes	-		86·5 (SD 6·7)	88·7 ± 6·3†	67/ 89	75%	68/ 90	75%
Foss (2009)[32]	-	Denmark	120	Patients with hip fracture	80 v 100	> 65	81 (SD 7·3)	81 ± 6·8†	46/ 60	77%	46/ 60	77%
Fan (2014)[33]	-	China	186	Patients who had had total hip replacement	80 or symptomatic v 100	> 65	75 (SD 6)	73 ± 7†	64/ 94	68%	59/ 92	64%
Studies including younger patients												
Carson (2011, 2015)[30,31]	FOCUS	USA	2016	Patients with hip fracture and who were at cardiovascular risk or disease	80 or symptomatic v 100	≥ 50	81·5 (SD 9·0)	81·8 ± 8·8†	239/ 1009	76%	250/ 1007	75%
Carson (2013)[35]	MINT	USA	110	Patients with cardiac catheterisation, acute coronary syndrome, or stable angina	80 or symptomatic v 100	> 18	74·3 (SD 11·1)	67·3 ± 13·6†	28/ 55	51%	27/ 55	49%
So-Osman (2013)[36]	-	Netherlands	603	Patients who had had primary or revision total hip or knee surgery	Varied by hospital, risk level, time after surgery	≥ 18	70·7 (SD 9·6)	70·2 ± 10·3†	190/ 299	64%	211/ 304	69%
Nakamura (2015)[37]	Substudy of TRACS	Brazil	260	Cardiac surgery patients aged ≥60 years	80 v 100	Compared < 60 v ≥60	68 (SD 6)	70 ± 6†	49/ 125	39%	47/ 135	35%
de Almeida (2015)[38]	-	Brazil	198	Patients with active cancer and had elective and emergency surgery	70 v 90	≥ 18	64 (SD 12)	64 ± 14†	46/ 101	46%	42/ 97	43%
Murphy (2015)[39]	TITRe 2	UK	2003	Patients with cardiovascular disease who had non-emergency cardiac surgery	75 v 90	> 16	70·8 (IQR 64-77)	69·9, 63-76‡	307/ 1000	31%	323/ 1003	32%

Data for age range are mean (SD) or median (IQR). TRIFE=transfusion requirements in frail elderly. FOCUS=functional outcomes in cardiovascular patients undergoing surgical hip fracture repair. MINT=myocardial ischemia and transfusion. TRACS=transfusion requirements after cardiac surgery. TITRe2=transfusion indication threshold reduction.

Table 1: Characteristics of randomized controlled trials included in meta-analysis

Five (63%) of eight studies reported composite outcomes for cardiac complications, whereas three (37%) reported specific cardiovascular events (appendix p 6). Meta-analysis of composite cardiac complications showed significantly better outcomes with liberal transfusion compared with restrictive transfusion (RR 1·62, 95% CI 1·12–2·35; p=0·010; figure 3), whereas there was no significant difference between transfusion strategies for myocardial infarction (1·50, 95% CI 0·97–2·33; p=0·069; figure 3).

Eight (89%) of nine RCTs reported a range of composite and specific infection outcomes (appendix p 7). Data for these specific outcomes were accumulated and used for meta-analysis (figure 4). The application of restrictive or liberal transfusion strategy did not affect infection incidence in these studies (RR 0·99, 95% CI 0·88–1·10; p=0·80).

Two (33%) of six studies reported length of hospital stay using means and SDs, whereas four (67%) studies reported medians and IQRs (appendix p 7). To facilitate meta-analysis, medians were equated to means and IQRs were converted to SDs. However, the alternative reporting approaches are represented as different subgroups in the meta-analysis (figure 5). The mean and SD group (mean difference –0·53, 95% CI –1·48 to 0·41; p=0·27), median and IQR group (0·06, –0·19 to 0·32; p=0·63), and combination of both groups (0·02, –0·22 to 0·27; p=0·86) all did not reach significance. Therefore, length of hospital stay was unrelated to transfusion strategy.

A moderate degree of heterogeneity[40] was observed between the studies reporting 30-day mortality (I^2=59%), and infection incidence (46%). Low-to-moderate heterogeneity was seen for composite cardiac complications (38%), and low heterogeneity for composite length of hospital stay (23%). The outcomes of 90-day mortality (0%) and myocardial infarction (0%) were homogeneous (table 2).

To examine the effect of including RCTs with a proportion of younger patients, the three RCTs limited to patients aged 65 years and older[6,32,33] were used in subgroup analyses (appendix pp 7–9). The two RCTs that reported risk of mortality at 30 days[6,32] showed significantly better outcomes for patients who followed a liberal transfusion strategy than for those who followed a restrictive transfusion strategy (RR 2·07, 95% CI 1·09–3·92; p=0·026). Composite cardiac complications (2·31, 0·61–8·77; p=0·22), infection incidence (1·01, 0·86–1·19; p=0·91), and overall length of hospital stay (mean difference of the composite measure 0·11, 95% CI –0·67 to 0·89; p=0·78) outcomes were not significant in the subgroup analyses. Only one of these geriatric-specific RCTs reported 90-day mortality[6] and none reported myocardial infarction outcomes; therefore, a subgroup analysis was not possible. The small number of studies and patients in these subgroup analyses should be noted.

	Number of studies	Number of patients	RR (95% CI)*	Mean difference (95% CI)†	Test for overall effect		I^2 (%)
					Z	p value	
Primary outcomes							
30-day mortality	7	4969	1·36 (1·05–1·74)	..	2·38	0·017	59%
90-day mortality	2	2287	1·45 (1·05–1·98)	..	2·29	0·022	0
Secondary outcomes							
Composite cardiac complications‡	5	1367	1·62 (1·12–2·35)	..	2·57	0·010	38%
Myocardial infarction	3	4090	1·50 (0·97–2·33)	..	1·81	0·069	0
Infection incidence	8	5402	0·99 (0·88–1·10)	..	0·26	0·80	46%
Length of hospital stay							
Mean and SD group	2	306	..	–0·53 (–1·48 to 0·41)	1·10	0·27	0
Median and IQR group	4	3088	..	0·06 (–0·19 to 0·32)	0·48	0·63	40%
Composite of mean and median groups	6	3394	..	0·02 (–0·22 to 0·27)	0·18	0·86	23%

RRs were generated with the Mantel-Haenszel method, with use of a fixed effects model. Mean differences were generated with the inverse variance method, with use of a fixed effects model. RR=risk ratio. *RR >1·0 favours liberal transfusion strategy. †Mean difference >0 favours liberal transfusion strategy. ‡Composite cardiac complications included cardiac failure, patients with cardiogenic shock, and major cardiovascular events.

Table 2: Comparison of restrictive versus liberal transfusion strategies against primary and secondary outcomes

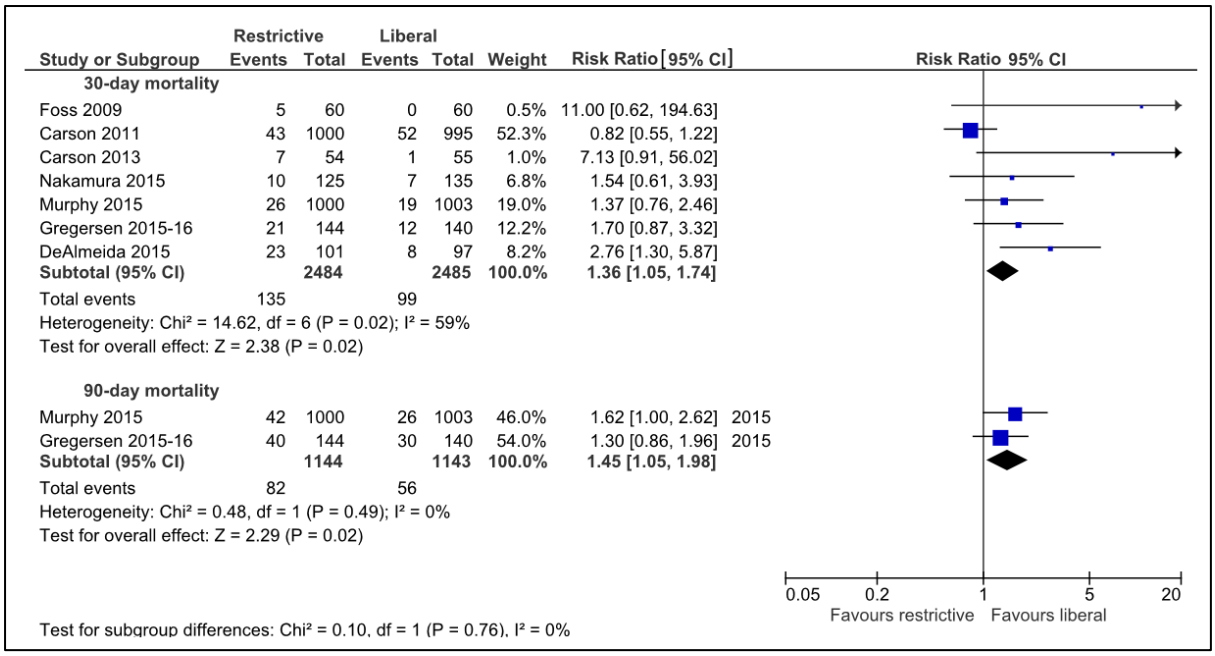

Figure 2: **Comparisons of restrictive versus liberal transfusion strategies against primary outcomes of 30-day and 90-day mortality**
RRs were generated with the Mantel-Haenszel method, with use of a fixed effects model. RR=risk ratio.

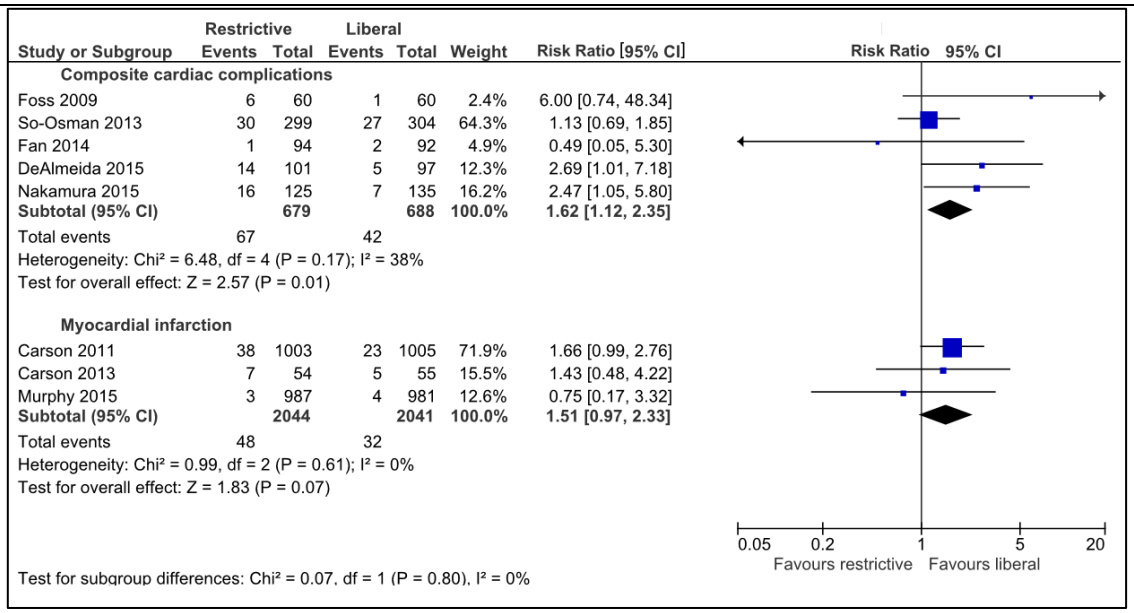

Figure 3: Comparisons of restrictive versus liberal transfusion strategies against secondary outcomes of composite cardiac complications and myocardial infarction
RRs were generated with the Mantel-Haenszel method, with use of a fixed effects model. RR=risk ratio.

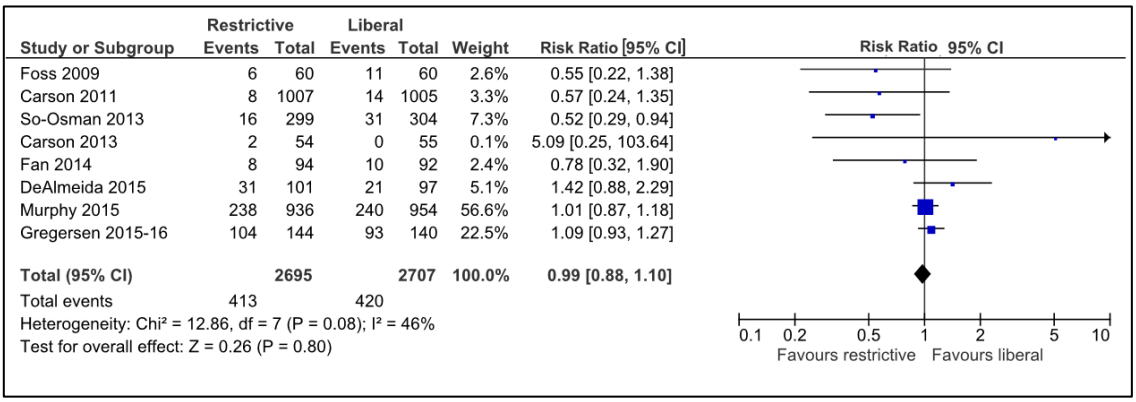

Figure 4: Comparisons of restrictive versus liberal transfusion strategies against secondary outcome of infection incidence
RRs were generated with the Mantel-Haenszel method, with use of a fixed effects model. RR=risk ratio.

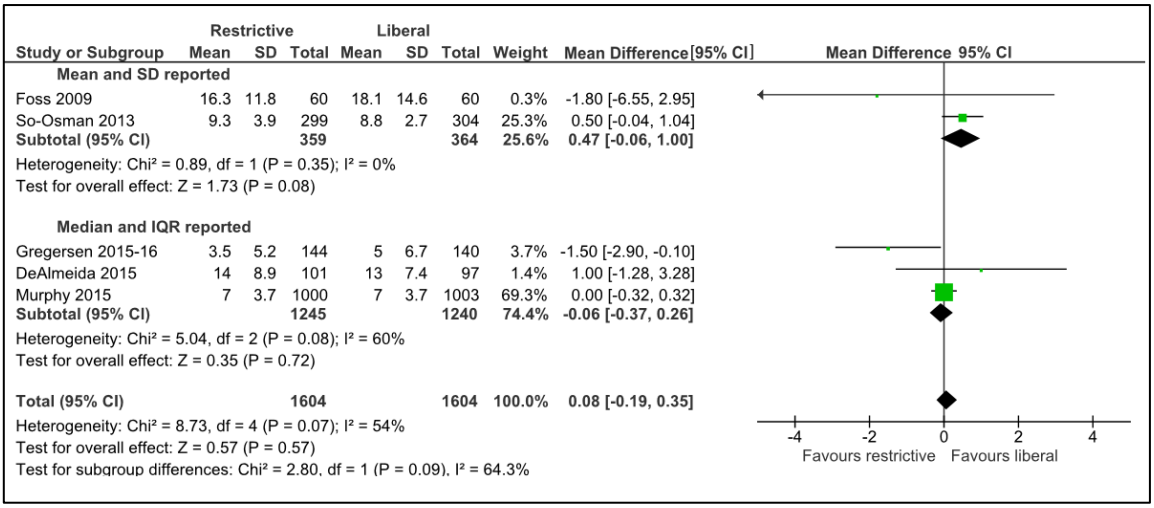

Figure 5: Comparisons of restrictive versus liberal transfusion strategies against secondary outcomes of length of hospital stay
Data for medians were equated to means and IQRs converted to SDs for meta-analysis. Data are reported as different subgroups of mean and SD, median and IQR, and an overall composite of both of these subgroups. Mean differences were generated with the inverse variance method, using a fixed effects model.

Original article published online (www.thelancet.com/haematology) September 11, 2017
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Discussion

The meta-analysis of nine RCTs that focused on transfusion outcomes in older patients identified that a liberal rather than a restrictive transfusion strategy provided improved outcomes with respect to 30-day mortality, 90-day mortality, and composite cardiac complications. In these studies, transfusion strategy did not affect the infection incidence or influence length of hospital stay. The risk of myocardial infarction was lower in the liberal strategy cohort, but analysis did not reach significance. The conclusions of this meta-analysis contrast with findings of most observational studies and some RCTs.[7,41] This meta-analysis highlights the importance of considering age and clinical or surgical discipline when defining study cohorts and interpreting outcomes.

The landmark 1999 transfusion requirements in critical care (TRICC) trial[42] compared restrictive (haemoglobin threshold <70 g/L) and liberal (haemoglobin threshold <100 g/L) transfusion strategies in patients older than 18 years. This trial raised substantial questions regarding the safety of liberal transfusion and the need to maintain higher haemoglobin concentrations in critically ill patients, and was instrumental in challenging transfusion practice. It is worth noting that subgroup analysis of the TRICC trial subsequently identified that a restrictive transfusion strategy was associated with lower mortality in patients younger than 55 years, but this effect was not seen in older patients.[7,42]

RCTs yielded by our search strategy are in accordance with the method used in the TRICC trial in comparing restrictive and liberal transfusion strategies. However, haemoglobin thresholds varied between studies, with cohorts of restrictive transfusion strategy ranging from 70 g/L to 97 g/L and liberal transfusion strategy spanning from 90 g/L to 113 g/L (table 1). Therefore, the definition of a restrictive haemoglobin threshold in one study might be higher than the liberal threshold in another, potentially confounding outcome comparisons and complicating deliberation of haemoglobin thresholds for transfusion.

The transfusion requirements after cardiac surgery (TRACS) trial[36] compared outcomes for patients aged 60 years and older with those younger than 60 years. Although the incidence of cardiogenic shock was greater in the restrictive than in the liberal transfusion group for older patients, this effect was not seen in the younger group. The authors proposed that reduced physiological reserve and an increased number of comorbidities might account for the increased age-based risk seen in this study. Hence, studies that include younger patients might mask outcomes for older participants unless age-stratified subgroup analysis is done.

Older patients might exhibit different outcomes with liberal transfusion than younger adults because of age- related differences in anaemia risk and effect. Studies have shown that younger patient populations have a greater tolerance of anaemia, and have a wider safety margin for a decrease in haemoglobin concentrations.[11] Elderly patients with their decline in physiological reserve and different responses to blood loss and anaemia are at increased risk from anaemia generally, as well as in the postoperative period.[11] This risk is manifested in outcomes such as increased incidence of postoperative decline in cognitive function and cardiac complications associated with anaemia.[11,43] Some studies report that transfusion is

protective of the myocardium at low haemoglobin concentrations, and others report protective effects against delirium in older patients.[25,32,36,44] Postoperative delirium, in turn, is found to be associated with increased lengths of hospital stay, poor functional outcomes, and increased rates of ongoing care requirements.[21]

There are several limitations associated with this study. We found a paucity of RCTs that focused on older patients. Wide confidence intervals are reported for a small number of study findings. These findings were in smaller studies with few events; therefore, they had low weightings in the calculation of overall effect. Additionally, the quantity of peer-reviewed data available might be limited by publication bias. Studies with negative findings might remain unpublished, and therefore be missing from the peer-reviewed literature. We did not include data from trials that had a mean age of patients of less than 64 years, although such studies might include a substantial proportion of older patients. Because of the small number and sample size of RCTs focused on patients aged 65 years and older, we have included studies with a broader recruitment strategy, increasing the age heterogeneity of the population studied. Although the subgroup analysis of studies restricted to patients aged 65 years and older reached significance with respect to 30-day mortality, this finding included only a small number of studies and patients. Only one oncology study was identified, and outside cardiac and orthopaedic surgery we did not identify other specialty areas with data available. The restrictive and liberal haemoglobin thresholds used across the studies are non-standard, potentially confounding analysis. Because of the small number of studies, we were unable to do a subgroup analysis by disease or treatment type. This study should therefore be seen as exploratory. We also observed heterogeneity in our findings. Factors that might have contributed to this heterogeneity include inconsistent haemoglobin thresholds used for restrictive and liberal transfusion groups, different clinical presentations across the patient groups, and the range of patient ages being represented, with some studies including younger patients despite the mean study age being 64 years or older.

Blood transfusion is often a marker for greater severity of illness.[7,8,28,41] Sicker patients are therefore likely to receive transfusions and be transfused at increased haemoglobin concentrations to address symptoms. Hence the association between higher numbers of transfusion and worse outcomes might be a reproducible artifact of observational study designs. Our analysis of data on older patients does not support the conclusions often reported in observational studies of increased morbidity, mortality, and lengths of hospital stay being associated with higher incidence of transfusion. Instead, it finds that restrictive transfusion practice is associated with higher incidence of mortality and cardiac morbidities in the older patient groups.

Paediatric patients are recognised in patient blood management guidelines as having unique requirements because of their physiology, but little recognition has been given to the effect of physiological differences in the geriatric population.[45] The absence of specific guidelines for older adults is notwithstanding the substantially greater use of blood and blood products by geriatric patients.[17,18] Outstanding questions in geriatric care that have not been adequately addressed include fluid management and ideal transfusion thresholds.[46] Key areas that need to be considered in transfusion decision making include the effect of anaemia on geriatric patients, altered physiological responses in the older patient that affect their ability to respond to blood loss or mask their clinical condition, and issues of frailty and

disability. The findings of our meta- analysis raise questions about the application of restrictive transfusion practice in older patients, and confirm the need to generate geriatric-specific evidence to inform revisions of patient blood management guidelines.

Contributors

All authors contributed to the development of the study protocol.

GIS did the literature search and meta-analysis. GIS produced the first draft, including tables and figures. All authors contributed to reviewing and editing the final version. GIS had responsibility for final submission of the Article.

Declaration of interests

We declare no competing interests.

Acknowledgments

This study was funded by Australia's National Blood Authority under a research and development grant (grant agreement ID 104).

References

1. Carson JL, Guyatt G, Heddle NM, et al. Clinical practice guidelines from the AABB: red blood cell transfusion thresholds and storage. *JAMA* 2016; **316:** 2025–35.
2. National Blood Authority. Patient blood management guidelines: module 1; critical bleeding/massive transfusion. Canberra: National Blood Authority, 2011.
3. National Blood Authority. Patient blood management guidelines: module 2; perioperative. Canberra: National Blood Authority, 2012.
4. National Blood Authority. Patient blood management guidelines: module 3; medical. Canberra: National Blood Authority, 2012.
5. National Blood Authority. Patient blood management guidelines: module 4; critical care. Canberra: National Blood Authority, 2012.
6. Gregersen M. Postoperative red blood cell transfusion strategy in frail anemic elderly with hip fracture. A randomized controlled trial. *Dan Med J* 2016; **63:** B5221.
7. Mirski MA, Frank SM, Kor DJ, Vincent JL, Holmes DR Jr. Restrictive and liberal red cell transfusion strategies in adult patients: reconciling clinical data with best practice. *Crit Care* 2015; **19:** 202.
8. Willett LR, Carson JL. Management of postoperative complications: anemia. *Clin Geriatr Med* 2014; **30:** 279–84.
9. Nydegger UE, Luginbuhl M, Risch M. The aging human recipient of transfusion products. *Transfus Apher Sci* 2015; **52:** 290–94.
10. Prince MJ, Wu F, Guo Y, et al. The burden of disease in older people and implications for health policy and practice. *Lancet* 2015; **385:** 549–62.
11. Kulier A. Blood conservation in geriatric patients. *Infus Ther* 2001; **28:** 99–100.
12. Zhao FZ, Wolf SE, Nakonezny PA, et al. Estimating geriatric mortality after injury using age, injury severity, and performance of a transfusion: the geriatric trauma outcome

score. *J Palliat Med* 2015; **18:** 677–81.
13. Ercin E, Bilgili MG, Sari C, et al. Risk factors for mortality in geriatric hip fractures: a compressional study of different surgical procedures in 785 consecutive patients. *Eur J Orthop Surg Traumatol* 2017; **27:** 101–06.
14. Llewelyn CA, Taylor RS, Todd AA, Stevens W, Murphy MF, Williamson LM. The effect of universal leukoreduction on postoperative infections and length of hospital stay in elective orthopedic and cardiac surgery. *Transfusion* 2004; **44:** 489–500.
15. National Blood Authority. Patient blood management guidelines: module 6; neonatal and paediatrics. Canberra: National Blood Authority, 2016.
16. Goel R, Cushing MM, Tobian AA. Pediatric patient blood management programs: not just transfusing little adults. *Transfus Med Rev* 2016; **30:** 235–41.
17. Allden RL, Sinha R, Roxby DJ, Ireland S, Hakendorf P, Robinson KL. Red alert—a new perspective on patterns of blood use in the South Australian public sector. *Aust Health Rev* 2011; **35:** 327–33.
18. Tinegate H, Pendry K, Murphy M, et al. Where do all the red blood cells (RBCs) go? Results of a survey of RBC use in England and North Wales in 2014. *Transfusion* 2016; **56:** 139–45.
19. Bosch MA, Contreras E, Madoz P, et al. The epidemiology of blood component transfusion in Catalonia, Northeastern Spain. *Transfusion* 2011; **51:** 105–16.
20. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6:** e1000097.
21. Blandfort S, Gregersen M, Borris LC, Damsgaard EM. Blood transfusion strategy and risk of postoperative delirium in nursing homes residents with hip fracture. A post hoc analysis based on the TRIFE randomized controlled trial. *Aging Clin Exp Res* 2017; **29:** 459–66.
22. Gregersen M, Borris LC, Damsgaard EM. Postoperative blood transfusion strategy in frail, anemic elderly patients with hip fracture: the TRIFE randomized controlled trial. *Acta Orthop* 2015; **86:** 363–72.
23. Gregersen M, Damsgaard EM, Borris LC. Blood transfusion and risk of infection in frail elderly after hip fracture surgery: the TRIFE randomized controlled trial. *Eur J Orthop Surg Traumatol* 2015; **25:** 1031–38.
24. Carson JL, Terrin ML, Noveck H, et al. Liberal or restrictive transfusion in high-risk patients after hip surgery. *N Engl J Med* 2011; **365:** 2453–62.
25. Carson JL, Sieber F, Cook DR, et al. Liberal versus restrictive blood transfusion strategy: 3-year survival and cause of death results from the FOCUS randomised controlled trial. *Lancet* 2015; **385:** 1183–89.
26. The Cochrane Collaboration. Review Manager (RevMan). Computer program. Version 5.3. Copenhagen: The Nordic Cochrane Centre, 2014.
27. Higgins J, Green S. 9.4.4.1 Mantel–Haenszel methods. 2011. http://handbook-5-1.cochrane.org/chapter_9/9_4_4_1_mantel_ haenszel_methods.htm (accessed May 14, 2017).
28. Carson JL, Carless PA, Hébert PC. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. *Cochrane Database Syst Rev* 2012; **4:** CD002042.
29. Carson JL, Stanworth SJ, Roubinian N, et al. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. *Cochrane Database Syst Rev*

2016; **10:** CD002042.
30. Higgins J, Green S. 7.7.3.5 medians and interquartile ranges. 2011. http://handbook-5-1.cochrane.org/chapter_7/7_7_3_5_mediansand_ interquartile_ranges.htm (accessed May 14, 2017).
31. Higgins J, Green S. 10.4.3.1 recommendations on testing for funnel plot asymmetry. 2011. http://handbook-5-1.cochrane.org/ chapter_10/10_4_3_1_recommendations_on_testing_for_funnel_ plot_asymmetry.htm (accessed July 15, 2017).
32. Foss NB, Kristensen MT, Jensen PS, Palm H, Krasheninnikoff M, Kehlet H. The effects of liberal versus restrictive transfusion thresholds on ambulation after hip fracture surgery. *Transfusion* 2009; **49:** 227–34.
33. Fan YX, Liu FF, Jia M, et al. Comparison of restrictive and liberal transfusion strategy on postoperative delirium in aged patients following total hip replacement: a preliminary study. *Arch Gerontol Geriatr* 2014; **59:** 181–85.
34. Carson JL, Brooks MM, Abbott JD, et al. Liberal versus restrictive transfusion thresholds for patients with symptomatic coronary artery disease. *Am Heart J* 2013; **165:** 964–71.
35. So-Osman C, Nelissen R, Brand R, et al. The impact of a restrictive transfusion trigger on post-operative complication rate and well-being following elective orthopaedic surgery: a post-hoc analysis of a randomised study. *Blood Transfus* 2013; **11:** 289–95.
36. Nakamura RE, Vincent JL, Fukushima JT, et al. A liberal strategy of red blood cell transfusion reduces cardiogenic shock in elderly patients undergoing cardiac surgery. *J Thorac Cardiovasc Surg* 2015; **150:** 1314–20.
37. de Almeida JP, Vincent JL, Galas FR, et al. Transfusion requirements in surgical oncology patients: a prospective, randomized controlled trial. *Anesthesiology* 2015; **122:** 29–38.
38. Murphy GJ, Pike K, Rogers CA, et al, for the TITRe2 Investigators. Liberal or restrictive transfusion after cardiac surgery. *N Engl J Med* 2015; **372:** 997–1008.
39. Higgins J, Altman D, Sterne J, the Cochrane Statistical Methods Group and the Cochrane Bias Methods Group. Chapter 8: assessing risk of bias in included studies. 2011. http://handbook-5-1.cochrane. org/chapter_8/8_assessing_risk_of_bias_in_included_studies.htm (accessed May 14, 2017).
40. Higgin J, Thompson S, Deeks J, Altman D. Measuring inconsistency in meta-analysis. BMJ 2003; 327: 557–60.
41. Carson JL, Terrin ML, Magaziner J, et al. Transfusion trigger trial for functional outcomes in cardiovascular patients undergoing surgical hip fracture repair (FOCUS). Transfusion 2006; 46: 2192–206.
42. Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med 1999; 340: 409–17.
43. Sulpice L, Rayar M, Campillo B, et al. Advanced age remains an achilles heel for liver resections. World J Surg 2014; 38: 918–26.
44. van der Zanden V, Beishuizen SJ, Scholtens RM, de Jonghe A,de Rooij SE, van Munster BC. The effects of blood transfusion on delirium incidence. J Am Med Dir Assoc 2016; 17: 748–53.
45. Heffernan DS, Thakkar RK, Monaghan SF, et al. Normal presenting vital signs are

unreliable in geriatric blunt trauma victims.J Trauma 2010; 69: 813–20.
46. Coburn M, Rohl AB, Knobe M, Stevanovic A, Stoppe C, Rossaint R. Anesthesiological management of elderly trauma patients.Der Anaesthesist 2016; 65: 98–106.