

Postoperative red blood cell transfusion strategy in frail anemic elderly with hip fracture

PhD dissertation

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Preface and acknowledgement

This PhD dissertation is based on studies carried out during my employment at the Department of Geriatrics, Aarhus University Hospital during the period 2010 to 2014.

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Merete Gregersen, 2015

List of abbreviations

ADL	Activities of Daily Living
ASA	American Society of Anesthesiologist
BMI	Body Mass Index
CAM	Confusion Assessment Method
CAS	Cumulated Ambulation Score
CCI	Charlson Comorbidity Index
CI	Confidence Interval
CGA	Comprehensive Geriatric Assessment
CRP	C-reactive protein
CVD	Cardiovascular Disease
DL	Depression List
EVF	Erythrocyte volume fraction
GP	General Practitioner
Hb	Hemoglobin
HRQoL	Health Related Quality of Life
INR	International Normalized Ratio
IQR	Interquartile Range
MBI	Modified Barthel Index
NMS	New Mobility Score
NSAID	Non-Steroidal Anti-Inflammatory Drug
OQoL	Overall Quality of Life
QoL	Quality of Life
RBC	Red Blood Cell
RCT	Randomized Controlled Trial
SD	Standard Deviation
UTI	Urinary Tract Infection

Conversion factors

Hemoglobin concentration:

- Multiply by 1.61 to get from millimol per liter (mmol/L) to gram per deciliter (g/dL)
- Multiply by 0.62 to get from g/dL to mmol/L ¹

Hematocrit value

-“10/30 rule” e.g. hemoglobin 10 g/dL (6.2 mmol/L) = hematocrit is approximately 30% ²

List of papers

- Paper I **Postoperative blood transfusion strategy in frail anemic elderly with hip fracture: the TRIFE randomized controlled trial.** Gregersen M, Borris LC, Damsgaard EM. Acta Orthop. 2015. Jan 14:1-10.
- Paper II **Blood transfusion and risk of infection in frail elderly after hip fracture surgery: the TRIFE randomized controlled trial.** Gregersen M, Borris LC, Damsgaard EM. Eur J Orthop Surg Traumatol. 2015 Feb 18.
- Paper III **Blood transfusion and Overall Quality of Life after hip fracture in frail elderly: the TRIFE randomized controlled trial.** Gregersen M, Borris LC, Damsgaard EM. J Am Med Dir Assoc. 2015

(Appendix 2)

The red color is warm and reminds us of love and lifeblood
The red blood is giving life to our bodies by pumping through our veins
The blood is giving life for our souls

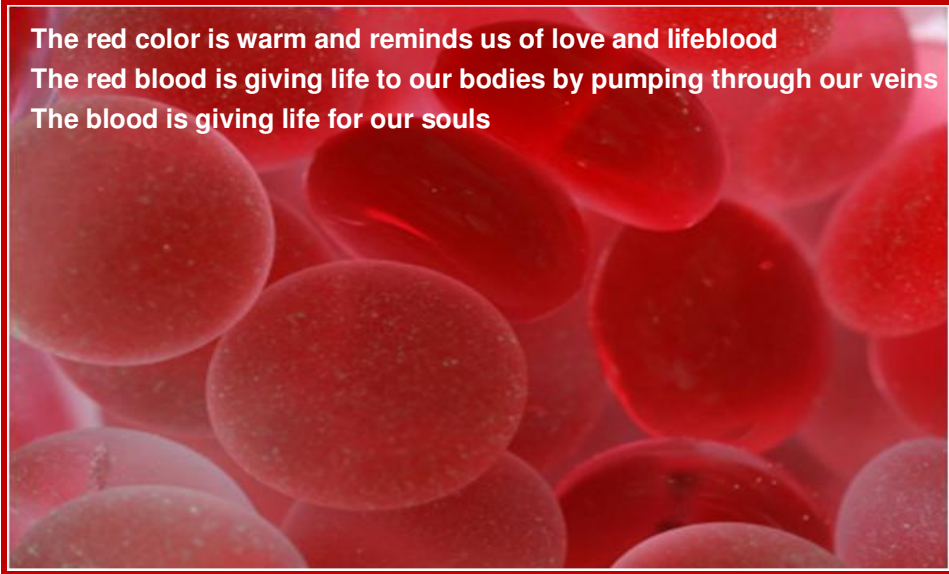


Illustration: Red blood cells

In memory of Johanne Augusta Gregersen

- my dear grandmother who died shortly after hip fracture surgery

Introduction

In the years 2003 to 2005, a high mortality rate was observed in hip fracture patients from nursing homes discharged from Aarhus University Hospital [3]. At that time, nursing home residents were discharged a few days after surgery and without geriatric follow-up. Therefore in 2006, the Geriatric Department initiated a standardized geriatric follow-up in the patient's residence after the hospitalization. In 2008, this service was expanded to a more tailored intervention. In the context "Early discharge - hospital at home", the tailored geriatric intervention was brought into focus immediately after discharge [4]. A hospital-based multidisciplinary geriatric specialist service in the municipalities had the task of improving continuity of care across the sector line in the healthcare system. The postoperative interventions in the nursing home residents were, among others, focusing on medical evaluation including pain management, fall diagnosing, treatment of osteoporosis, early mobilization, nutritional supplementation, fluid therapy, and a liberal red blood cell (RBC) transfusion strategy. This transfusion strategy was a hemoglobin threshold of 7 mmol/L (11.3 g/dL) which was higher than the threshold of 6 mmol/L (9.7 g/dL) recommended by the Danish National Guidelines [5]. We found that the tailored intervention seemed to improve recovery from physical disability, and furthermore reduced 30-day mortality from 19% to 8% compared with a standardized follow-up. The most important differences between the standardized and the tailor-made follow-up methods were 1) patients were visited when needed instead of at fixed schedule and 2) a more liberal transfusion strategy that brought the hemoglobin value up to 7 mmol/L was followed. However, it seemed important to examine which part of the intervention was responsible for the crucial improvement in recovery from physical disability and in reducing mortality.

The present PhD study is a continuation of these findings. A hip fracture can have fatal consequences for the physically and cognitively impaired older adult [6]. It is well known that the probability of 30-day mortality is associated with age and comorbidity [7]. Hip fracture surgery is associated with blood loss, and anemia is associated with poor patient outcomes [8]. A large number of observational studies have compared outcomes in transfused patients with non-transfused patients, but many of these studies are limited by lack of adjustment of confounding variables or biased by potential unmeasured or unknown confounders [9]. By minimizing bias and confounding problems through randomization, many experimental studies have examined a restrictive RBC transfusion strategy in comparison with a liberal strategy, with the aim of saving RBC products

without harming the anemic patients [10]. These experimental studies, characterized by mixed patient populations with varying age, disabilities, and diseases, do not offer much attention to the frail elderly hip fracture patient from a nursing home who has low functional abilities and high risk of mortality. Therefore it is necessary to examine only the frail elderly in such a way that important patient outcomes did not disappear in the large diverse populations.

Background for the PhD project and existing literature

Anemia in the elderly

Anemia is a decreased concentration of hemoglobin (Hb) in the blood in a normally hydrated and euvolemic person [11].

The definition of anemia according to World Health Organization (WHO) [194]

- ❖ Female: Hb concentration in the blood < 7.5 mmol/L (12 g/dL)
- ❖ Male: Hb concentration in the blood < 8.1 mmol/L (13 g/dL)

The Hb concentration is lower on average in people of older age. With advancing age in normal adults, Hb decline around 0.03 to 0.06 g/dL annually, with men suffering a faster fall. Yet, this modest fall does not result in anemia in most people [12]. The prevalence of anemia in the elderly hospitalized patient or nursing home resident ranges between 35% and 54% [13-16], and is associated with poor physical performance [14,15]. In prevalent anemia (*chronic*), conditions such as certain infections, inflammatory diseases, kidney diseases, thyroid disease, peptic ulcer, and cancer are important causes via immune-driven processes [17-19]. Incident anemia (*acute*) is a condition in which the amount of red blood cells suddenly drops, e.g. due to blood loss in surgical procedures, drains or gastrointestinal bleeding. Incident anemia increases the heart rate, but does not affect the blood pressure [20]. Clinical signs such as tachycardia, cyanosis or pallor and cool, clammy skin will suggest a diagnosis of anemic hypoxia after acute blood loss. Oxygen (O₂) delivery to the peripheral tissues is proportionally dependent on three factors: the cardiac output, the arterial O₂ saturation, and the arterial Hb concentration which in turn is dependent on the concentration of red blood cells in the plasma, since almost all Hb molecules are located inside the red blood cells [21].

Functional impairments and Quality of Life

Anemia is a powerful prognostic factor for the development of frailty manifest in the form of muscle weakness, reduced physical performance, and falls [12]. Patients with anemia have a lower rate of recovery from physical disability than those with a normal Hb level [22,23]. Functional recovery and self-scored energy level after hip repair increase with higher Hb levels, which were independently associated with increased walking distance [24]. *Nursing home residents* with Hb levels between 6.2 and 6.8 mmol/L (10 and 11 g/dL)

had significantly worse ADL functioning than residents with a level above 8 mmol/L (13 g/dL) [15]. Anemia is associated with impaired handgrip strength and knee extensor strength, and it increases the risk of fall [25,26]. Furthermore, anemia increases the risk of incident dementia [27]. Cognition score, measured by MMSE, in the anemic elderly is lower than subjects who have normal Hb levels [28]. Studies of nursing home residents found a positive correlation between cognitive function score and Hb levels [13,29]. Postoperative anemia is associated with delirium [30] and anemia in the elderly is associated with worse health-related Quality of Life (HRQoL) ratings [29]. Elderly long-term care residents with a Hb less than 10 g/dL have a significantly lower HRQoL than those with the >13 g/dL reference value [31,32].

Acute anemia predicts:

- ❖ Impaired ADL recovery
- ❖ Risk of fall
- ❖ Reduced handgrip and knee extensor strength
- ❖ Delirium
- ❖ Health-related Quality of Life
- ❖ Mortality

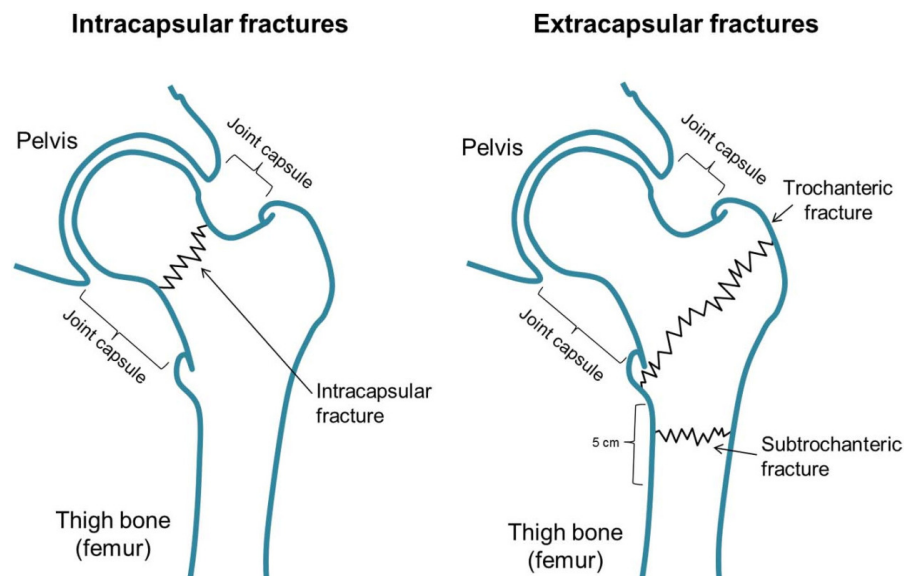
Mortality

In the community-based population, *prevalent anemia* significantly predicts hospitalization and mortality [8]. In the hospitalized geriatric patients and in the nursing home residents, anemia is related to both 3-month and 6-month mortality [33-35]. By *incident anemia* the risk of 30-day mortality becomes extremely high in elderly Jehovah's Witness patients with Hb level below 3.7 mmol/l (6 g/dL). Below this level, a compensation for a reduced oxygen-carrying capacity is no longer adequate, and leading to ischemia and death [36]. In patients with cardiac vascular disease (CVD) there is a trend toward an increased mortality when Hb value is below 5.9 mmol/L (9.5 g/dL) as compared with patient with other diagnoses [37]. Mortality declines steadily with increasing EVF value (hematocrit), and the greatest risk of 30-day mortality was seen with an admission EVF value between 5% and 24% [2,38]. Low Hb concentration represents underlying diseases when causes of death in older anemic persons most often are due to malignant neoplasms or infections, and not due to aging [19,39].

Hip fracture

Hip fracture in the proximal part of the femur occurs most frequently in the elderly population, and approximately 72% of the hip fracture patients are women [40,41]. Mean age at the first hip fracture at the first hip fracture is 80 years for men, and 81 years for women.

Figure 1 Types of hip fractures.



The hip fractures are distributed with 54% femoral neck (intercapsular), 40% trochanteric, and 6% subtrochanteric fractures [42] (extracapsular), and are placed as seen in Figure 1. Hip fractures are primarily caused by fall related to osteoporosis [40]. Hip fractures are most often treated surgically by arthroplasty or internal fixation. Hip fractures account for 9% of the Danish population, and the incidence rate of the first hip fracture has fallen in both sexes as also noted in other Western countries [42].

Postoperative complications

Prevalent anemia at admission is found in 43-46 % of the hip fracture patients and is associated with the development of postoperative complications [34,40,43]. Perioperative blood loss leading to acute anemia is common in patients with hip fracture [44]. A significant decrease in Hb level is found in elderly Norwegian hip fracture patients: preoperative from average 7.4 mmol/L (12 g/dL) to postoperative 5.6 mmol/L (9 g/dL) [45]. Arthroplasty is associated with a risk of a greater blood loss than internal fixation

[46]. In hip fracture patients the frequency of postoperative red blood cell (RBC) transfusions varies between 48% and 69% [4,23,47,48]. RBC transfusions in pre-fracture independent-walking hip fracture patient are median 2 RBC units (IQR: 0-3) per patients [23].

Incident anemia is associated with an increasing risk of nosocomial infections [49]. A postoperative Hb level below 6.2 mmol/L (10 g/dL) is associated with complications such as UTI, pneumonia, and myocardial infarction [45]. Urinary tract infection (UTI) is the most frequent infection after hip fracture surgery, approximate 26% of the elderly acquire a UTI [49]. Pneumonia is the most common postoperative complication in men, and UTI is most common in women [50]. Arthroplasty leads to longer operation time, significantly fewer postoperative complications, and fewer re-operations [46,51]. Advanced age is not related to number and type of complications after hip fracture [52].

Most frequent postoperative complications after hip fracture surgery:

- ❖ Acute anemia
- ❖ Urinary tract infection
- ❖ Pneumonia
- ❖ Wound infection
- ❖ Delirium
- ❖ Pain
- ❖ Acute gastrointestinal hemorrhage

Within 30 days after surgery, approximately 30% of the hip fracture patients develop a state of delirium [53]. A prolonged incidence of delirium (≥ 4 weeks) is found to be associated with poor functional outcome and increased mortality [53]. The risk of delirium increases with advanced age and a postoperative Hb level below 6.2 mmol/L (10 g/dL) in elderly admitted from institutional care, and in demented elderly [45]. Acute gastrointestinal hemorrhage (bleeding peptic ulcer) occurs in 3.9 % of the patients with hip fracture and is an independent predisposing factor, especially in those with co-morbidities and in NSAID treatment [54,55]. Peptic ulcer increases blood loss and mortality [56].

Recovery from physical disabilities

Postoperative anemia in hip fracture patients is associated with decreased ambulation, reduced functional independence, and reduced walking distance on discharge [24,57]. Patients with a Hb level below 6.2 mmol/L (10 g/dL) have a significant lower ambulation score on the second and third postoperative day [23]. Functional recovery and self-scored

energy level after hip fracture repair increases with higher Hb levels, and a higher postoperative Hb level is independently associated with walking greater distance [24].

Advanced age is strongly associated with poor recovery of both ADL and ambulation after hip fracture [58]. In the youngest elderly, recovery peaks at 6 months, but recovery in the oldest old continues for 12 months [58]. Hip fracture in nursing home residents is associated with substantial loss of functional independence and ambulation [59]. Pre-fracture functional level is found to be a strong and consistent predictor of short- and long-term rehabilitation outcomes in hip fracture patients [35,60-64], and comorbidities have a negative impact on mobility and ADL recovery [65]. Moreover, cognitive impairments seem to negatively influence the outcome of patients with hip fracture [45,66] even though the cognitively impaired have the same potential of successful rehabilitation as non-cognitively impaired who were pre-fracture mobile [67,68].

Cervical fractures are associated with better functional outcome than trochanteric fractures [60,69,70], and for patients with cognitive impairment, hemiarthroplasty provides a better functional outcome compared to internal fixation [71]. Patients receiving an arthroplasty have less pain postoperatively than patients with internal fixation, but after 1 year no difference in pain is found [46,71,72].

Predictors of poor recovery from physical disability after hip fracture surgery:

- ❖ Acute anemia
- ❖ Prevalent anemia
- ❖ Advanced age
- ❖ Impaired prefracture functional level
- ❖ Comorbidities
- ❖ Cognitive impairment
- ❖ Internal fixation compared to arthroplasty
- ❖ Trochanteric fractures compared to cervical

Quality of Life

To perform ADL more independently after hip fracture repair appears to speed up recovery in some QoL areas [73]. However, hip fracture patients report a lower overall QoL even before the fracture occurred, and they seem to be less satisfied with life as a whole [59,74,75]. Twelve months after hip fracture surgery, elderly with internal fixation reports a lower QoL than patients with arthroplasty [71] whereas the opposite is the case when QoL is assessed by proxies [75]. Norwegian nursing home residents report a lower HRQoL score than the general population in Norway [76] and frail nursing home residents report a lower HRQoL than non-frail residents [77]. Yet, people with dementia seem to have a

more positive outlook on their lives and roles than their caregivers have [78,79]. Elderly with dementia are able to express views about their QoL, even in the later stages of their illness [78,80-82].

In elderly patients undergoing elective orthopedic surgery, red blood cell (RBC) transfusions and hemoglobin (Hb) levels at discharge are not associated with QoL within the first 2 weeks postoperatively [83]. However, in the randomized controlled trial (RCT) in which this finding was made; Hb values were not significantly different in patients treated according to a restrictive versus those treated according to a liberal RBC transfusion strategy. In a prospective observational study in elderly patients after primary hip arthroplasty, Conlon et al. found a positive correlation between Hb levels on discharge and changes in QoL scores from preoperatively to 2 months after surgery [84]. Furthermore, studies in older patients have demonstrated associations between prevalent (chronic) anemia and HRQoL [29,31]. Elderly long-term care residents with a Hb less than 10 g/dL have a significant lower health related (HR) QoL than patients with the >13 g/dL reference [15,32].

In elderly hip fracture patients physical measurements are highly correlated with HRQoL [85]. Patients with good mobility (no walking aid or just one stick) have significantly better QoL scores than those with poorer mobility (walker or wheel chair) [86]. Hip fracture patients report a lower overall QoL even before the fracture occurred [59,74], and 12 months after hip fracture both QoL and physical functional status are decreased in the nursing home residents compared to prefracture status [59].

Mortality

Hip fractures have the highest rate of mortality of all of the fragility fractures [69,87-90]. Overall mortality is 23-29% during the first year after hip fracture, and hip fracture patients have a 2 to >3-fold risk of *1-year mortality* compared to persons without hip fracture [91-96]. During the first 3 postoperative months, elderly with hip fracture have a 5- to 8-fold increased risk for death compared to a matched group of elderly without hip fracture [70] and *3-month mortality* rate varies between 5% and 24% [45,50,89]. In Denmark, the *30-day mortality* rate is 11% in >65-year-old hip fracture patients [97]. The inability to stand up and sit down and the inability to walk 2 weeks after surgery are strong predictors for mortality [98]. Besides, being 85 years or older and having cognitive impairment are associated with a higher incidence of mortality in elderly hip fracture patients [45,50,96].

Predictors of mortality after hip fracture surgery:

- ❖ Chronic anemia
- ❖ Acute anemia
- ❖ Advanced age
- ❖ Male sex
- ❖ Comorbidities
- ❖ Cognitive impairment
- ❖ ADL dependency (pre-fracture)
- ❖ Inability to walk (pre-fracture)
- ❖ Trochanteric fracture compared to cervical
- ❖ Depression
- ❖ Surgery delay
- ❖ A previous hip fracture
- ❖ Residential status
- ❖ Polypharmacy

Men with hip fracture have a higher cumulative mortality than women, despite men being on average 4 years younger at the time of fracture [6,35,45,50,63,65,66,96,99-101]. Men are more likely to suffer from most comorbidities included in the Charlson Index, especially pronounced for malignancy, cardiac heart failure, chronic obstructive pulmonary disease, and all forms of arterial diseases [101]. Comorbidities and chronic anemia are associated with both in-hospital and 6-month mortality [34,65,102,103]. Depression and dementia in the elderly with hip fracture significantly increase the risk of 1-year mortality [104].

There is no significant difference in short-term or long-term mortality between arthroplasty and internal fixation [51]; however, mean survival is slightly longer after a femoral cervical fracture than after a trochanteric fracture [101,105]. Moreover, timing matters in hip fracture surgery. A meta-analysis that included 191,873 patients found that a surgical delay of 24/48 hours or more increases the risk of death [106]. The risk of death for patients admitted during weekends or on public holidays was not found to be higher [107]. The anesthetic technique does not seem to have a major impact on postoperative mortality [108]. The mortality rate after a second hip fracture is significantly increased [41].

In all hip fracture patients, the most important causes of death seem to be related to cardiac and pulmonary factors, and dementia [6,90,109,110]. Death is in theory found to be potentially avoidable in 57% of the elderly hip fracture patients who die [89].

Red blood cell transfusions

RBC transfusions are typically used to provide an immediate correction of incident anemia and operative hemorrhage. Transfusions improve the oxygen-carrying capacity, but they may not be effective in all patients [111,112]. Anemia at admission is the most useful predictor of RBC transfusion risk during hospitalization [44,113]. A Danish observational study of consecutively hip fracture patients aged 60+ years and found that female gender, increasing age, admitted from residential care, increasing ASA score, extracapsular fractures, low admission Hb, use of aspirin or other platelet inhibitors at admission were all significantly associated with RBC transfusion [114].

The Danish Health and Medicine Authority's recommendation for RBC transfusion until 2014 was:

- ❖ hemoglobin threshold of 6 mmol/L (9.7 g/dL)

or on occurrence of symptoms of anemia in younger patients with normal heart and lung function, the RBC transfusion could be postponed to Hb concentration of 4.5 mmol/L (7.2 g/dL) [158].



Infections

Transfusions are thought to cause a reduction in the recipient's immune response [115]. Immunomodulating effects may increase the risk of developing nosocomial infections, acute lung injury, and autoimmune diseases later in life [115]. This is particularly an important issue in critically ill, injured, and postoperative patients. Several cohort studies, comparing patients who received blood transfusion with those who were not transfused, have examined the potential association between allogeneic blood transfusion and postoperative bacterial infections [116]. In most of the observational studies, it was found that RBC transfusion increased the risk of postoperative bacterial infections defined as bacteremia, pneumonia, deep wound infection, or sepsis [49,115,117-121], whereas other observational studies found no such associations [54,91]. In a prospectively observational study of 1349 patients, RBC transfusions were found to be a significant independent predictor of postoperative wound infections and intra-abdominal sepsis in colorectal surgery [118]. Potential confounders to surgical site infections are length of surgery, tobacco use, diabetes, and preoperative anemia [121].

Mortality

In both critically ill patients and surgery patients, RBC transfusion is found to be associated with increased overall mortality when comparing transfused with non-transfused [115,119,122]. However, among patients younger than 80 years, RBC transfusions do increase the risk of death within 6 months, but in patients above 80 years transfusions did not increase either 6-months or 3-years mortality [123]. RBC transfusions are associated with mortality, but when adjusted for baseline characteristics and confounding variables such as age, gender, residential status, and preoperative Hb level, transfusion was no longer associated with 120-day mortality or 1-year mortality [91]. In patients with community-acquired severe sepsis and septic shock, RBC transfusions are common. Adjusting for possible confounding factors and severity of illness, transfusions in these patients are associated with lower risk of 28-day mortality [124]. In CVD patients there is a disproportionate increase in mortality with increasing anemia [37,125], and in elderly patients with acute myocardial infarction, whose erythrocyte volume fraction (EVF) on admission fell into the categories ranging from 5-24%, RBC transfusion was associated with a reduction in 30-day mortality [38]. Mortality in hip fracture patients receiving 'old' units of blood (>14 days) do not differ from those receiving 'new' units [126].

RBC transfusion strategies

The use of erythrocyte components has been the standard care for treating anemia for more than 100 years and considered as simple and harmless to the patients [127]. Researchers began to question the evidence behind this practice in the 1990s, and in the latest decade many trials and meta-analysis have been performed aiming at saving blood without impairing clinical outcomes. Denmark spent in 2008, 67 units of blood per 1,000 inhabitants, and the rate has remained at roughly the same high level for over 20 years [97]. Most research studies conclude that a restrictive RBC transfusion strategy is to be advised. RCTs and meta-analyses have compared restrictive strategies with liberal strategies in various patient populations according to age, prefracture abilities, and diseases (Table 1). Hb targets in restrictive strategies are in the range of 4.3 to 5.6 mmol/L (7-9 g/dL) but transfusion can be given if signs and symptoms indicate anemia. Hb targets in liberal strategies are in the range of 5.6 to 6.2 mmol/L (9-10 g/dL) [72,128-142].

A meta-analysis combined nine of the RCTs, and concluded that a lower Hb threshold of minimum 4.3 mmol/L (7 g/dL) does not adversely affect 30-day or 60-day

mortality, physical recovery or infection rates [10]. In hip fracture patients, a large multicenter study from USA/Canada found no difference in short-term mortality, physical recovery, or infection rates [137]. Another recent meta-analysis found that a restrictive RBC transfusion strategy was associated with a reduced risk of serious infection compared to a liberal strategy [143]. Thus, RBC resources can be saved.

However, in all these experimental studies regarding optimal thresholds for RBC transfusions, the frail elderly hip fracture patients were mixed with the overall study population in which the results for solely this frail population disappeared, or the frail elderly was totally excluded from the studies, although we in the literature found that:

- ❖ Being 85 years or older and having cognitive impairment are associated with a higher incidence of mortality [45,50,96]
- ❖ Nursing home residents with Hb levels between 6.2 and 6.8 mmol/L (10 and 11 g/dL) had significantly worse ADL functioning than residents with a level above 8 mmol/L (13 g/dL) [15].
- ❖ Anemia in the frail elderly is related to 3-months mortality [34,35]
- ❖ The risk of delirium increases in association with: advanced age, postoperative Hb level less than 6.2 mmol/L (10 g/L), residential status, and state of dementia [30,45,144]
- ❖ Delirium is associated with poor functional recovery after hip fracture and with death [144,145]
- ❖ Postoperative Hb level less than 6.2 mmol/L (10 g/dL) is associated with complications such as UTI, pneumonia, and myocardial infarction [45,49]
- ❖ Pneumonia is associated with death [35]
- ❖ In patients above 80 years, RBC transfusions do not increase either 6-month or 3-year mortality [123]
- ❖ In severely ill CVD patients a liberal RBC transfusion strategy seems to reduce mortality [37,146]
- ❖ Frail elderly patients who undergo surgery are more likely to encounter postoperative complications (e.g. pneumonia, delirium, and UTI), prolonged hospital stays, institutionalization, and higher mortality rates [147]
- ❖ Frailty is associated with adverse outcomes including fall, postoperative complications, delayed recovery, morbidity, disability, and mortality [148-151]

Table 1 Randomized controlled trials and meta-analyses concerning red blood cell (RBC) transfusion strategies in chronological order (1/6)

Study	Patients and setting	Postoperative intervention		Outcomes			Conclusion
		Restrictive target	Liberal target	Physical ability	Mortality	Infection	
Bush 1997 California, USA RCT ^	99 patients undergoing elective major arterial reconstructions in an intensive care unit. Mean age: 65 years	Hb level 5.6 mmol/L (9 g/dL) Period: 48 hours	Hb level 6.2 mmol/L (10 g/dL) Period: 48 hours	NR	30-day mortality: No difference (8% vs. 8%)	NR	A lower threshold was tolerated without clinical adverse outcome. Quality of study: 8/10
Carson 1998 Scotland RCT ° ^ Pilot study	80 hip fracture patients without symptoms of anemia and hospitalized in an orthopedic department. Mean age: 82 years	Hb level 5 mmol/L (8 g/dL) or by symptoms of anemia (chest pain, congestive heart failure, and unexplained tachycardia or hypotension unresponsive to fluid replacement) Period: 6.3 days (±3.4)	Hb level 6.2 mmol/L (10 g/dL) Period: 6.4 days (±3.4)	At 60 days: "Death or inability to walk across the room without assistance": No difference (39% vs. 45%)	30-day mortality: No difference (2.4% vs. 2.4%) 60-day mortality: No difference (11.9% vs. 4.8%)	Pneumonia during hospital stay: No difference (0% vs. 4.8%)	A restrictive strategy may be an effective blood-sparing protocol associated with fewer RBC transfusions. Quality of study: 7/10
Bracey 1999 Texas, USA RCT ° ^	428 elective primary coronary bypass graft surgery patients in an intensive care unit. Mean age: 61 years	Hb level 5 mmol/L (8 g/dL) or if clinical conditions requires RBC transfusion Period: 5 days	Hb level 5.6 mmol/L (9 g/dL) Period: 5 days	NR	In-hospital mortality (median 7 days): No difference (2.7% vs. 1.4%)	No difference (2% vs. 1%)	By lowering the Hb threshold did not adversely affect the patient outcomes. Quality of study: 8/10
Hébert 1999 Canada RCT ° ^ * 'TRICC study'	838 critically ill patients admitted to intensive care unit Mean age: 58/57years	Hb level 4.3 mmol/L (7 g/dL) Period: 11.3 days (±11.3)	Hb level 6.2 mmol/L (10 g/dL) Period: 11 days(±10.7)	NR	In-hospital mortality: Statistical significant difference (22.2% vs. 28.1%) 30-day mortality: No difference (19% vs. 23%) 60-day mortality: No difference (23% vs. 27%)	Pneumonia: No difference (21% vs. 21%)	A restrictive strategy is at least as effective as a liberal strategy with a possible exception of patients with acute myocardial infarction and unstable angina. Quality of study: 9/10

Table 1, *continued* 2/6

Study	Patients and setting	Postoperative intervention		Physical ability	Outcomes		Conclusion
		Restrictive target	Liberal target		Mortality	Infection	
Lotke 1999 Pennsylvania, US RCT [^]	152 total knee arthroplasty patients in a department of orthopedic surgery. Mean age: 69 years	Hb level 5.6 mmol/L (9 g/dL) of autologous blood	Immediately 2 units of autologous blood after surgery	NR	30-day mortality: No difference (0% vs. 0%)	NR	Patient who received immediate transfusions had fewer nonsurgical complications. Quality of study: 7/10
Hebert 2001 Canada RCT	357 critically ill patients with cardiovascular diseases and a Hb less than 4.3 mmol/L (7 g/dL) from the TRICC study. Mean age: 65 years	Hb level 4.3 mmol/L (7 g/dL) Period: 9.2 days (\pm 11.6)	Hb level 6.2 mmol/L (10 g/dL) Period: 11.3 days (\pm 9)	NR	30-day mortality: No difference (23% vs. 23%) 60-day mortality No difference (26% vs. 27%)	NR	A restrictive RBC transfusion strategy appears to be safe in most critically ill patient with CVD with the possible exception of patients with acute myocardial infarcts and unstable angina. Quality of study: 9/10
Grover UK 2006 RCT ^{o ^} Multicenter	218 patients undergoing elective hip and knee replacement surgery across seven hospitals. Mean age: 71 years	Hb level 5 mmol/L (8 g/dL) Period: 5 days	Hb level 6.2 mmol/L (10 g/dL) Period: 5 days	NR	14-day mortality: No difference (0.6% vs. 0.3%)	NR	The study did not achieve statistical power to conclude. No difference in incidence of silent myocardial ischemia. Quality of study: 4/10
Lacroix 2007 Canada RCT ^{o ^ *} 'TRIPICU study'	637 critically ill children in a pediatric intensive care unit. Mean age: 3 years	Hb 4.3 mmol/L (7 g/dL) Period: 2.3 days (\pm 1.8)	Hb 5.9 mmol/L (9.5 g/dL) Period: 2.3 days (\pm 1.7)	NR	28-day mortality: No difference (4% vs. 4%)	Nosocomial infections: No difference (25% vs. 20%)	A restrictive threshold can decrease RBC transfusion requirements without increasing adverse outcomes. Quality of study: 9/10
Foss 2009 Denmark RCT ^{o ^}	120 hip fracture patients with independent prefracture walking function and intact cognitive status hospitalized in a hip fracture unit. Mean age: 81 years	Hb level 5 mmol/L (8 g/dL) or if an acute cardiac condition indicated a liberal strategy Period: 17 days (\pm 12.9)	Hb level 6.2 mmol/L (10 g/dL) Period: 18.4 days (\pm 14)	The first three postoperative days no difference in CAS was found	30-day mortality: Statistical significant difference (8% vs. 0%)	In-hospital pneumonia: No difference (2% vs. 3%) Sepsis: (2% vs. 2%) Wound infection: (0% vs. 5%)	A liberal transfusion trigger did not result in increased ambulation scores. A restrictive threshold should be treated with caution in the elderly. Quality of study: 8/10

Table 1, continued 3/6

Study	Patients and setting	Postoperative intervention		Physical ability	Outcomes		Conclusion
		Restrictive target	Liberal target		Mortality	Infection	
So-Osman 2010 Netherlands RCT °	603 patients admitted to three different orthopedic wards for elective hip- and knee replacement surgery. Mean age: 70 years Subgroup: High risk group (n=416), age 70+ years and high comorbidity.	<u>≤ 4 h of surgery:</u> If Hb < 5.6 mmol/L (8.9 g/dL) =1 RBC unit If Hb < 5.1 mmol/L (8.1 g/dL)=2 RBC units If Hb < 4.5 mmol/L (7.2 g/dL)=3 RBC units <u>After 4 h of surgery</u> If Hb < 6.1 mmol/L (9.7 g/dL) =1 RBC unit If Hb < 5.6 mmol/L (8.9 g/dL)=2 RBC units If Hb < 5.1 mmol/L (8.1 g/dL)=3 RBC units Period: 9.6 days (±5)	Hb level 6.0 mmol/L (9.7g/dL) Hb level 6.5 mmol/L (10.5 g/dL) Period: 10.2 days (±7)	NR	14-day mortality No difference (0.6% vs. 0.3%)	No difference (6% vs. 10.1%)	Implementation of a uniform transfusion protocol for elective lower joint arthroplasty patients is feasible, but does not always lead to a RBC reduction. Quality of study: 5/10
Hajjar 2010 Brazil RCT ° 'TRACS study'	512 adults who underwent cardiopulmonary bypass surgery in an intensive care unit. Mean age: 59 years	Hematocrit 24% Hb 5.7 mmol/L (9.2 g/dL) Period: 12 days (IQR 9-21)	Hematocrit 30% Hb 6.6 mmol/L (10.6 g/dL) Period: 12 days (IQR 9-20)	NR	30-day mortality: No difference (6% vs. 5%)	Infectious complications: No difference (12% vs. 10%)	The use of a restrictive strategy compared to a liberal resulted in non-inferior rates of outcomes. Quality of study: 8/10
Cooper 2011 RCT ° Pilot study	45 anemic patients with acute myocardial infarct. Mean age: 76/70 years	Hematocrit 24% Hb 5 mmol/L (8 mmol/L) Period: 10.4 days (±7.2)	Hematocrit 30% Hb 6.6 mmol/L (10.6 g/dL) Period: 8.5 days (±5.6)	NR	In-hospital mortality: No difference (8% vs. 5%) 30-day mortality: No difference (8% vs. 5%)	NR	A liberal strategy may be associated with worse clinical outcome when death is combined with recurrent AMI or new or worsening heart failure. Quality of study: 5/10

Table 1, continued 4/6

Study	Patients and setting	Postoperative intervention		Outcomes			Conclusion
		Restrictive target	Liberal target	Physical ability	Mortality	Infection	
Carson 2011 USA / Canada RCT ° Multicenter FOCUS study	2016 hip fracture patients with high-risk factors for cardiovascular disease and able to walk independently before fracture occurred. Mean age: 82 years	Hb level 5 mmol/l (8 g/dL) or symptoms of anemia Period: USA: 4 days (±3.9) Canada: 13 days (±9.5)	Hb level 6.2 mmol/L (10 g/dL) Period: USA: 4 days (±3.4) Canada: 12 days (±9.3)	Inability to walk independently: No difference (43.8% vs. 40.9%)	30-day mortality: No difference (4.3% vs. 5.2%) 60-day mortality: No difference (6.6% vs. 7.6%)	Wound infection: No difference (0.8% vs. 1.4%)	Inability to walk independently and mortality was not reduced by a restrictive transfusion strategy. Quality of study: 9/10
Carson 2012 New Jersey, USA Meta-analysis	19 trial involving 6264 critically ill, trauma- and surgery patients.	Hb levels range between 4.3 - 5.6 mmol/L (7-9 g/dL)	Hb levels range between 5.6 - 6.2 mmol/L (9-10 g/dL)	Lower extremity physical ADL at 30 days (1 trial): No difference Lower extremity physical ADL at 60 days (1 trial): No difference	In-hospital mortality: (5 trials) Statistical significant difference (6.5% vs. 8.6%) 30-day mortality: (11 trials) No difference 60-day mortality: (3 trials) No difference	Pneumonia: (5 trials) No difference (8% vs. 8.7%) Infections: (6 trials) No difference (8.4% vs. 10.3%)	Restrictive transfusion strategies did not appear to impact the rate of adverse events compared to liberal transfusion strategies and did not reduce functional recovery. Quality of study: 9/10
Shehata 2012 Canada RCT ° Pilot study	50 high-risk cardiac surgery patients. Mean age: 67/69 years	Hb level 4.7 mmol/L (7.5 g/dL) Period: 9 days	Hb level 6.2 mmol/L (10 g/dL) Period: 7 days	NR	In-hospital mortality: No difference (16% vs. 4%)	Pneumonia: No difference (16% vs. 0%) Sepsis: No difference (12% vs. 0%)	Low adherence. The Hb measures in the two groups were statistically significant different. Few participants. Quality of study: 7/10
Villanueva 2013 Spain RCT ° *	921 acute upper gastrointestinal bleeding patients admitted to hospital aged 18+ years Mean age: 65 years	Hb level 4.3 mmol/L (7 g/dL) + 1 unit of RBC was transfused initially. Period: NR	Hb level 5.6 mmol/L (9 g/dL) + 1 unit of RBC was transfused initially. Period: NR	NR	45-day mortality: Statistical significant difference (5% vs. 9%)	Bacterial infections: No difference (27% vs. 30%) Pneumonia: No difference (10% vs. 11%)	A restrictive strategy significantly improved outcomes. Further bleeding was reduced. Quality of study: 8/10

Table 1, *continued* 5/6

Study	Patients and setting	Postoperative intervention		Outcomes			Conclusion
		Restrictive target	Liberal target	Physical ability	Mortality	Infection	
Carson 2013 USA RCT ° Pilot-study	110 patients with acute coronary syndrome or stable angina undergoing cardiac catheterization in eight US hospitals. Mean age: 70.8 years	Symptoms related to anemia or Hb level 5 mmol/L (8 g/dL) Period: NR	1 unit of RBCs was transfused initially. Hb level 6.2 mmol/L (10 g/dL) Period: NR	NR	30-day mortality: Statistical significant difference (13% vs. 1.8%)	NR	Patient transfused using restrictive strategy had more than 2 times the rate of death, myocardial infarction or revascularization. Quality of study: 7/10
Parker 2013 UK RCT	200 hip fracture patients aged 60+ years with no cognitive impairments and Hb level between 5 mmol/L (8 g/dL) and 5.9 mmol/L (9.5 g/dL) the first two days after surgery. Mean age: 84 years	Transfusion if symptoms of anemia were found: vaso-vagal episodes on mobilization, chest pain of cardiac origin, congestive cardiac failure, unexplained tachycardia, hypotension, or dyspnoea.	Median 2 units of RBCs to raise Hb to a level of 6.2 mmol/L (10.0 g dL/L) or above.	No difference in mean change measured by New Mobility Score within 8 weeks from discharge	30-day mortality: No difference (5% vs. 3%) 90-day mortality: No difference (11% vs. 10%)	NR	No difference in outcome related to transfusion. Quality of study: 5/10
Salpeter 2014 New-York,USA Meta-analysis	3 trials of 2364 patients with critical illness or bleeding Mean age: 46 years	Hb level 4.3 mmol/L (7 g/dL) Period: during hospitalization	Hb level between 5.9 and 6.2 mmol/L (9-10 g/dL) Period: during hospitalization	NR	30-day mortality: Statistical significant difference (11% vs. 14%)	Bacterial infections: No difference (26% vs. 26%)	In patients with critically illness or bleeding, a restrictive strategy reduces cardiac events, re-bleeding and mortality Quality of study: 5/10
Rohde 2014 Michigan, USA Meta-analysis	18 trials of 7593 patients Cardiac, critical care, gastrointestinal bleeding, low birth weight, orthopedic, postpartum, sepsis, and sickle cell patients.	Hb level between 4 - 6 mmol/L (6.4 - 9.7 g/dL)	Hb level between 5.6 - 7 mmol/L (9 - 11.3 g/dL)	NR	NR	All counted infections: No difference (RR 0.92 (0.81-1.03)) Serious infections: Statistical significant difference (RR 0.84 (0.73-0.96))	Health care-associated infections were not associated with transfusion strategies, but the serious infections were. Quality of study: 8/10

Table 1, continued 6/6

Study	Patients and setting	Postoperative intervention		Physical ability	Outcomes		Conclusion
		Restrictive target	Liberal target		Mortality	Infection	
Holst 2014 Scandinavia Multicenter RCT	998 patients with septic shock in hospitals in Denmark, Sweden, Norway, and Finland. Median age: 67 years	Hb level 4.3 mmol/L (7 g/dL) Period: 28 days	Hb level 5.6 mmol/L (9 g/dL) Period: 28 days	NR	90-day mortality: No difference (43% vs. 45%)	NR	Similar mortality. No harm with an excess transfusion of a median of 3 units of blood. Quality of study: 9/10
Pinheiro de Almeida 2015 Brazil RCT	198 oncology patients, who had a major surgical procedure for abdominal cancer. Mean age: 64 years	Hb level 4.3 mmol/L (7 g/dL) Period: median 13 days	Hb level 5.6 mmol/L (9 g/dL) Period: median 14 days	NR	30-day mortality: Statistical significant difference (15.7% vs. 8.2%) 60-day mortality: Statistical significant difference (23.8% vs. 11.3%)	Abdomen infection: Statistical significant difference (14.9% vs. 5.2%) Pneumonia: No difference (7.2% vs. 7.9%) UTI: No difference (3.0% vs. 3.1%) Wound infection: No difference (3.0% vs. 4.1%)	A liberal transfusion strategy provides better outcomes than the restrictive. The restrictive strategy may not be as safe as previously perceived. Quality of study: 9/10

° RCTs included in the meta-analysis of Rohde et al.¹⁴³

^ RCTs included in the meta-analysis of Carson et al.¹⁰

* RCT included in the meta-analysis of Salpeter et al.¹⁵²

NR = not reported

Frail elderly

In the literature, there is no single best definition of frailty in the elderly. As a MeSH term in Medline, frailty is defined as “older adults or aged individuals who are lacking in general strength and are unusually susceptible to disease or to other infirmity”. The most commonly identified constructs of frailty are: decreased mobility, physical inactivity, aging, nutritional deficits, cognitive impairment, residential factors [148], and indoor falling [153].

As the aging population increases, it has becoming increasingly important to identify, which of the elderly are considered as frail. A clinical tool to assess frailty as a biologic syndrome can be used to differentiate between frailty, disability and co-morbidity [148]. In daily life among health care professionals, the *nursing home residents* and the *sheltered housing residents* are regarded as the frailest elderly. In Denmark, approximately 25% of the >65-year-old hip fracture patients are nursing home residents and 16% are sheltered housing residents [3]. Although sheltered housing residents are considered not as cognitive impaired as the nursing home residents and more independent in ADL, they also have medical or social needs to contend with. Both nursing homes and sheltered housing facilities provide 24-hour emergency help through alarm systems, with the care staff nearby.

In Denmark, two-thirds of the nursing home residents are cognitively impaired, half are dependent on personal ADL assistance, and 16% is undernourished (BMI <18.5) [154]. Pre-fracture status in hospitalized nursing home residents with hip fracture indicates that 21% have chronic anemia and 26% coronary arterial disease [35]. Nursing home residents have a greater risk of death following hip fracture than do home dwellers [63,155]. In Australia, the 30-day mortality rate following hip fracture in nursing home residents is 12%, and the 90-day mortality rate is 23%, rates that are very similar to the Danish mortality rates and that are nearly twice that of non-residents [155,156]. Approximately half of the residents with a hip fracture die within 12 months [59]. Infection and dementia in women and cardiac related diseases in men are the most common causes of death in nursing home residents [35].

Many studies agree that more attention to patients from nursing homes is needed in the health care system due to the frailty problem.

Systematic literature searches

The systematic literature search was performed according to the PICO-framework [157].

Limits: 2003-2014, Humans, Clinical Trials, Controlled Clinical Trials, Meta-analysis, Multicenter Study, Randomized Controlled Trial, Review, Systematic Review, Aged: 65+ years, Abstract [text] (Appendix 1, Table 1).

Research question

The standard recommendation of the RBC transfusion trigger has for many years been a liberal strategy with Hb level of 6.2 mmol/L (10 g/dL) or more. This trigger has been lowered within the last decade to Hb levels of 4.3-5.6 mmol/L (7-9 g/dL) because studies showed that a restricted strategy did not change the clinical outcome or even improved the outcome compared to the liberal transfusion strategy. In Denmark, the current recommendation for RBC transfusion treatment in acute anemic patients is based on this evidence regarding restricted use of blood components. Until 2014, a RBC transfusion was recommended when the Hb threshold was 6 mmol/L (9.7 g/dL) or there were symptoms of anemia, and in younger healthy patients with normal heart and lung function, the RBC transfusion could be postponed until the Hb concentration reached 4.5 mmol/L (7.2 g/dL) [158].

However, in the existing literature, research achievement concludes a high risk of fatal consequences in the elderly after hip fracture surgery. Furthermore, the combination of anemia and hip fracture is even more unfavorable. The most frail and vulnerable patients are the nursing home residents. Our previous observational study indicates that a liberal transfusion strategy might be favorable in nursing home residents combined with comprehensive geriatric assessment and other interventions after hip fracture repair. In a systematic literature search we found no experimental studies on RBC transfusion strategies in this frail population, but it should be noted that the frail elderly were part of a population that differed with regard to age, physical abilities and diseases, or the frail elderly were totally excluded from the studies.

Thus, it is necessary in an experimental design to examine whether the liberal RBC transfusion strategy in this frail population provides better patient outcomes than the restrictive strategy.

Aims

To examine whether a liberal strategy in Denmark for postoperative RBC transfusions in frail elderly with hip fracture from nursing homes and sheltered housing facilities

1. improves recovery from physical disabilities,
2. reduces short-term mortality,
3. is associated with treatment-requiring infections, and
4. enhances overall quality of life

as compared to the restrictive strategy recommended in Denmark.

Hypotheses

A *liberal* RBC transfusion strategy with a hemoglobin threshold of 7 mmol/L (11.3 g/dL) within the first 30 postoperative days after hip fracture surgery in patients admitted from nursing homes and sheltered housing facilities

1. improves ADL performance, ambulation, and mobility 10 days after hip fracture surgery, improves repeated Modified Barthel Index sum-scores measured preoperatively and three times during 90 postoperative days,
2. reduces the incidence of death measured at 30-day and 90-day follow-up,
3. increases the risk of treatment-requiring infections within 10 postoperative days,
4. increases the concentrations of leukocytes and C-reactive protein, measured in five repeated blood tests during 30 postoperative days, enhances OQoL sum-scores 30 days and 365 days after surgery, and OQoL progress is associated with ADL recovery

as compared to a *restrictive* strategy of 6 mmol/L (9.7 g/dL).

Methodologies

Randomized controlled trial

Design, participants and settings

Our study was named the TRIFE study (Transfusion Requirement In Frail Elderly). It was designed as a prospective, assessor blinded, randomized controlled trial. Eligible patients from the orthopedic surgical ward at Aarhus University Hospital were enrolled consecutively between January 18, 2010 and June 6, 2013. They comprised patients aged 65+ years admitted from nursing homes and sheltered housing facilities for unilateral hip fracture surgery, with postoperative Hb levels between 6 and 7 mmol/L (9.7–11.3 g/dL) during the first 6 postoperative days. If the Hb value was below 9.7 g/dL on the first day after surgery the patient was transfused according to the recommendations of the Danish Health and Medicine Authority for elderly hip fracture patients [5]. Patients' home-addresses declared their eligibility, which provided an unambiguous tool to recruit and allocate them to the two transfusion groups on admission to hospital. Hip fractures were categorized as three subtypes (International Code of Disease 10; ICD10) according to fracture line location: (i) femoral neck (ICD-10 S72.0); (ii) intertrochanteric (ICD-10 S72.1); and (iii) subtrochanteric (ICD-10 S72.2). Exclusion criteria were: active cancer, pathological hip fracture, inability to understand or speak Danish without an interpreter, RBC transfusion refusal (e.g., Jehovah's Witnesses), fluid overload, irregular erythrocyte antibodies, or previous participation in the trial.

Enrolments

Every day of the week the list of patients admitted to the orthopedic ward was scrutinized by the project manager to secure that all consecutively admitted patients were assessed for eligibility. All the patients with nursing home and sheltered housing addresses were recorded. The patient chart was reviewed to ensure the absence of active cancer, pathologic hip fracture, and immunization problems.

Ethical efforts

The trial was conducted in accordance with the ethical principles laid down in the Declaration of Helsinki. The Danish Data Protection Agency and The Ethical Committee of Central Denmark Region approved the protocol. Cognitive ability was measured by MMSE and CAM or assessed by two independent health care professionals, in all the eligible patients before participation was requested. Cognitively unimpaired was defined as patients

with a MMSE score >19 and no state of delirium, and written informed consent was obtained. Consent for cognitive impaired patients was given by a next of kin *plus* the relevant general practitioner (GP). If the GP was not available, the Ethical Committee of Central Denmark Region required that the Health Inspector in the Region was contacted to decide whether the patient could participate and to sign a surrogate consent. Half-yearly, an interim-analysis on the fatal outcomes was evaluated by an independent safety monitoring board. The study was registered at ClinicalTrials.gov, Identifier NCT01102010.

Randomization and blinding

After giving informed consent, patients were randomly assigned to either the *restrictive* RBC transfusion strategy (Hb <9.7 g/dL; 6 mmol/L) according to the national guidelines, or the *liberal* strategy (Hb <11.3 g/dL; 7 mmol/L) according to results of a previous observational study on tailored interventions that used the same liberal Hb criterion [4]. Randomization was provided by an allocation concealment process and conducted electronically in the web-based clinical-trial-support-system ‘TrialPartner’ developed by Public Health and Quality Improvement, Central Denmark Region. This central computer program using permuted block-sizes stratified the randomization according to gender and type of residence and allocated each participant to one of the transfusion strategies. The project manager entered the patient’s civil registration number into the computer program, and passed on the randomisation result to the electronic patient record which was available to the hospital staff in the orthopedic and geriatric wards because they would be administering the transfusions during the intervention period. The participants, their relatives and the endpoint assessors were blinded to the result of randomization. Information on the patients’ Hb measures was only available for the hospital staff.

RBC transfusion procedure

The standard venous Hb analysis was by cyanmethemoglobin assay (inter-laboratory error 0.2 g/dL) performed immediately upon admission and postoperatively [159]. Hb concentrations were measured daily during the first 3 postoperative days, then at least once during the following 4-6 days, and at least once per week during the subsequent 3 weeks. Erythrocyte volume fraction (EVF) was also measured at admission; however the Hb level decreases faster than the EVF and therefore the EVF is a more sensitive test to detect acute anemia [159]. RBC transfusions were performed when necessary according to group assignments and no later than 24 hours after the relevant Hb determination, and a further Hb measurement preceded each subsequent transfusion until the Hb target was reached. In acute situations, and between

transfusions, venous Hb levels were measured with a portable HemoCue photometer (HemoCue, Inc, Mission Viejo, CA, USA). No more than two units per day were administered. Adherence to the transfusion protocol was required for 30 days.

Figure 2 The HemoCue - a portable photometer.



In Denmark, one packed RBC unit comprises approximately 300 ml including 100 ml SAG-M (sodium chloride, adenine, glucose, and mannitol) and < 20 ml plasma and without functional thrombocytes or coagulation factors. In the suspension, the erythrocyte concentration is between 2.7 mmol/L and 4.8 mmol/L per unit. Leukocytes are reduced to < 1200 x 10⁶.

The suspension is collected from one donor. The red cells are separated from whole blood and stored in a citrate-phosphate-dextrose-adenine anticoagulant solution. The suspension is stored up to 5 weeks [160]. All patients received preoperative either 2000 mg intravenous dicloxacillin (a narrow-spectrum antibiotic of the penicillin class) or cefuroxime for patients

The transfusions were administered during hospitalization, in the nursing homes and in the sheltered housing facilities. A consultant geriatrician on the orthopedic ward prescribed the assigned RBC transfusion. After discharge the same geriatrician, who was member of the of the multidisciplinary orthogeriatric team that monitored patients after discharge from hospital, was still responsible for further prescription of RBC transfusions in the patients' residence as a standard procedure. During hospitalization, the hospital staff was responsible for administration of the RBC transfusions. After discharge, a physician or a nurse from the hospital's orthogeriatric team accomplished the transfusions in the patient's residence. Before each RBC transfusion it was mandatory to supply full information concerning available blood typing, irregular erythrocyte antibodies, and cross matching.

The designated blood unit was then transferred from the blood bank to the hospital ward, or the patient's residence, and stored in an authorized cool-box until use. Observations on body temperature, blood pressure, and pulse rate were registered. Two health care professionals secured the procedure by patient identification, tapping number, blood typing, and expiry date. In patients with cognitive impairment, the patient identification before the transfusion was verified by the staff in the residential homes or by the patient's relatives. The duration of the transfusion was approximately 1 hour. If the transfusion was provided at home, a nurse monitored the patient during the transfusion and at least 20 minutes after completion. After transfusion body temperature was re-measured and potential complications were

registered. The empty blood bag was stored in the ward 24 hours before it was discarded. If the RBC transfusion caused complication, the blood bag was returned to the blood bank [160].

Measurements

Cognitive status was assessed by:

- ❖ Mini-Mental State Examination (MMSE) ranging from 0-30 points. The sum score was categorized: normal cognitive ability=30-25, mild cognitive impairment=24-20, moderate impairment=19-11, severe impairment=10-5, and very severe cognitive impairment=< 5 [161]
- ❖ Confusion Assessment Method (CAM) (yes/no) assessing state of delirium [162]

Postoperative pain was assessed by:

- ❖ Verbal Rating Scale (VRS) comprising a list of adjectives used to denote increasing pain intensities: no pain=0, mild pain=1, moderate pain=2, severe pain=3, unbearable pain=4 [163]

Comorbidity was computed by:

- ❖ Charlson Comorbidity Index (CCI) evaluating the burden of comorbidity conditions [164]. With each increased level of the CCI, the cumulative mortality is attributable to comorbid diseases and increases in a stepwise fashion. CCI is found capable to predict 30-day mortality in elderly hip fracture patients [165] (low=0, moderate=1-2, high >2)
 - Cardiovascular diseases (CVD) were present if one of the first three options in the CCI is positive

Physical performance was assessed by:

- ❖ Modified Barthel Index (MBI) measuring the basic self-care ADL ranging from 0 to 100 points and assessing 10 domains: eating, transferring, personal care, toiletry, bathing, walking, managing stairs, dressing, bowel control, and bladder control (independent or moderate dependent=100-50, substantially dependent=49-25, completely dependent=24-0) [166]
 - Information on transferring from bed to chair independently (yes/no) was used separately.
- ❖ Cumulated Ambulation Score (CAS) measuring getting in and out of bed, sit-to-stand from a chair, and walking with or without an appropriate walking aid with a score ranging score from 0 to 6. Each activity was assessed on a 3-point scale from 0-2: not able to despite human assistance and verbal cueing=0, able to with human assistance and/or verbal cueing form one or more persons=1, able to safely, without human assistance or verbal cueing, use of a walking aid allowed=2 [167,168]

- ❖ New Mobility Score (NMS) assessing indoor walking ability, outdoor ability and ability to go shopping. Each activity is assessed on a 4-point scale from 0-3: not at all=0, with help from another person=1, with an aid=2, no difficulty=3 [169,170]
 - Information on indoor walking ability was used separately

Mortality:

- ❖ Date of death were obtained from the Civil Registration System in Denmark
- ❖ Causes of death were obtained from the Causes of Deaths Register, the Danish Ministry of Health.

Infection:

Defined as: “An infection occurring in a patient in a hospital or other health care facility in whom the infection was not present or incubating at the time of admission, and includes infections acquired in the hospital but appearing after discharge” [171]. The participants were screened daily by the health care professionals for any symptom suggesting infection.

- ❖ The number of infections within 10 days and 30 days after surgery were counted and divided into three categories: (i) pneumonia, (ii) urinary tract infection (UTI), (iii), and (iii) other infections including surgical wound infection, erysipelas, sepsis, pyelonephritis, and infections without focus.
- ❖ UTI was verified by microscopy, and pneumonia by stethoscopy and clinical assessment, and surgical wound infection were verified only by clinical assessment. When an infection was assessed by a physician, antibiotic treatment was initiated and the incidence of infection was noted in the electronic patient record.
- ❖ Infection biomarkers measured in blood samples and registered along with the Hb measurements on days 3, 10, 17, 24 and 30, or until death:
 - Leukocytes: white blood cells of the immune system that are involved in defending the body against infectious disease (normal count is between 3.5 to 10.0 x 10⁹/L)
 - C-Reactive Protein (CRP): An acute-phase protein in the blood plasma which rises in response to inflammation (normal < 8 mg/L)

Overall Quality of Life (OQoL) was assessed by:

- ❖ Depression List (DL), an interview-based questionnaire which is validated in nursing home residents. It can be completed by all residents with a MMSE-score as low as 5. The DL consists of 15 questions covering emotional well-being, social relationship, life-satisfaction, comfort, functional competence and autonomy. Along with each short and simple question, the keyword is presented on a card. For instance, the first item

‘Are you satisfied’ is accompanied by a card saying ‘satisfied’. The DL ranges from 0 point (=best OQoL) to 30 points (=worse) [80,172 (Appendix 1)].

After recruitment of all participants, frailty was evaluated:

Comprehensive Geriatric Assessment (CGA) Frailty Index. Participants were considered frail when fulfilling *one or more* of the following criteria: (i) dependency in ADL, (ii) severe comorbidity, (iii) cognitive dysfunction, (iv) malnutrition, (v) more than seven daily prescribed medications, or (vi) depression (Table 2) [150].

Table 2 Comprehensive Geriatric Assessment Frailty Index

Assessment	Frailty classification
ADL Modified Barthel Index (MBI) (range 0-100)	Prefracture dependency in ADL: MBI < 50
Comorbidity Charlson Comorbidity Index (range 0-30)	Severe comorbidity: CCI > 2
Cognitive function Mini Mental State Examination (MMSE) (range 0-30)	Cognitive dysfunction: MMSE < 20
Nutrition Se-albumin (g/l) and Body Mass Index (BMI)	Malnutrition: Albumin < 34 g/l and BMI < 18.5
Medication Number of daily prescribed medicines	Multimедication > 7
Depression Geriatric Depression Scale* (GDS)	GDS-score > 13

*Geriatric Depression Scale (range 0-30) was not included in the TRIFE frailty classification due to the acute situation. The depression assessment would be influenced by pain, the unsafe and unknown surroundings for the elderly patient.

Data collection and management

The *project manager* enrolled the participants and obtained the informed consents. The project manager also collected data on baseline characteristics, repeated blood measurements and infections from the patient chart and date of deaths. Data were collected in paper-form during the study period. Data were feed into the computer-program EpiData twice and errors in the dataset were corrected.

Two assessors were employed to assess the participants. On enrolment of each new participant, the assessor was advised and planned three visits during the 90 postoperative day period and a visit after 1 year (Figure 3). There was one assessor for each patient follow-up, and both assessors were blinded to the randomization assignment. The assessor collected information on pre-fracture abilities as they were experienced of the patient 14 days before the fracture. If the patients were unable to remember their own abilities, the caregivers or the relatives supplied this information.

Figure 3 PaT-plot of graphical depiction of intervention and measurements (above), with legend (below): Squares represent the orthogeriatric treatment and care, where the dark gray represents the blinded outcome assessor. Circles represent activities of the project manager. The 30-day postoperative intervention period in the geriatric ward or in the residence by the orthogeriatric team is shown in light gray.

Time Line	Restrictive group	Liberal group
Recruitment	(A) (B)	(A) (B)
Baseline	[C] [D]	[C] [D]
Randomisation	(E)	(E)
1 week	[F]	[F]
10 th postoperative day	[G] [H] (I)	[G] [H] (I)
17 th postoperative day	[G] [H]	[G] [H]
24 th postoperative day	[G] [H]	[G] [H]
30 th postoperative day	[G] [H] (I)	[G] [H] (I)
90 th postoperative day	[H] (I)	[H] (I)
365 th postoperative day	[H] (I)	[H] (I)

(A)	Daily identification of patients from nursing homes and sheltered housing admitted to orthopedic ward. Assessment of cognitive impairment and confusion.
(B)	Completion of informed consent or deputy informed consent
[C]	Preoperatively, all patients received 2000 mg intravenous dicloxacillin, a narrow-spectrum antibiotic of the penicillin class or cefuroxime in case of allergy to penicillin, and thromboprophylaxis..
[D]	Surgery
(E)	Computerized randomization and information of intervention handed over to hospital staff
[F]	Measurement of Hb level after surgery day: 1, 2, 3, and once between days 4 to 6 followed by the transfusion strategy
[G]	Measurement of Hb level followed by the transfusion strategy by the geriatric staff
[H]	Collection of measurements by a blinded outcome assessor (physical and cognitive ability, pain assessment, and overall quality of life)
(I)	Collection of outcomes by research coordinator of death, blood measures, and number of infections

Standard orthogeriatric care

The TRIFE study was incorporated in the orthopedic and geriatric teamwork (orthogeriatrics). Worldwide and during the last 20 years, several innovative orthogeriatric care models have been designed. According to the setting, care models are divided into: (i) acute in-patient orthogeriatric care, (ii) subacute rehabilitation, (iii) community-based rehabilitation, and (iv) early discharge hospital at home. The multidisciplinary approach with co-leadership has been shown to produce better outcomes for elderly hip fracture patients than traditional care, and a tailored intervention, leads to improved processes and outcomes for the hip fracture patients [4,64,173-177].

In the orthogeriatric team, the orthopedic surgeon is responsible for fracture management and surgery decisions, while the geriatrician is responsible for medical treatment and care based on Comprehensive Geriatric Assessment (CGA) [178]. CGA consists of several evaluation tools to explore the elderly patients' clinical, functional, cognitive, nutritional, and social domains and thereby obtaining a global picture to optimize the patient's long-term treatment, and to plan the resources required and the use of services [179]. CGA is widely used to detect disabilities and evaluate geriatric conditions that can be associated with frailty. Due to the varied type of geriatric approaches, it is difficult to draw firm conclusions about effectiveness. In some of the orthogeriatric models, there are effects concerning better functional recovery, shorter length of hospital stay, fewer complications, and reduced mortality [88,174], whereas other studies indicate improved efficiency, especially regarding delirium, recurrent falls and fractures, use of institutional care, and patient satisfaction [180,181]. Acutely ill, frail elderly patients have the best chance of survival if the patients undergo CGA [178].

In the preoperative phase, the multidimensional assessment is focused on performing the necessary surgery as quickly as possible and with the lowest possible risk [182]. The severity of coexisting chronic diseases is assessed by CGA to identify which of the comorbidities take the highest priority for treatment. CGA investigates the presence and intensity of pain to avoid insufficient treatment, assess the risk of delirium, and explores nutritional status. Early mobilization is established to reduce complications and physical disabilities [183].

Further assessments in the early post-operative phase are management of cognitive and behavioral issues to prevent the onset of delirium [53,184]. Maintaining an adequate nutritional status is another important aspect in the malnourished elderly patient [185]. Postoperative fluid therapy is standardized and intravenous or subcutaneous fluids are

administered if daily oral intake is insufficient. Oral iron treatment is also a standard and is prescribed after surgery if the patient has not already received treatment.

Orthogeriatric comprehensive assessments and interventions in elderly hip fracture patients:

- ❖ Early surgery
- ❖ Fall diagnosing
- ❖ Osteoporosis management
- ❖ Pain management
- ❖ Early mobilisation
- ❖ Nutritional supplementation
- ❖ Fluid therapy
- ❖ Antibiotic treatment
- ❖ Red blood cell transfusion
- ❖ Medical assessment
- ❖ Early discharge planning
- ❖ Training
- ❖ Home-safety
- ❖ Cross-sectorial and multidisciplinary

Planning early supported discharge and home-based rehabilitation service begins as close to the patient's hospital admission as possible and with involvement of the patient's family and caregivers from the nursing home and sheltered housing facilities [186]. The standard rehabilitation program is focused on ongoing medication evaluation to optimize or eliminate any unnecessary or harmful medication, hypotension treatment, pain management, and secondary prevention of fragility fractures, which includes reducing the risk of fall and improving bone quality [149,187]. Physical therapy, including balance, strength and endurance training, is performed [183]. The intervention is mostly based on recommendations of the National Board of Health, Accelerated Recovery Program after Hip Fracture [188], and the geriatric knowledge in bridge-building between hospital and municipality.

The day after surgery and according to residence status, residents from sheltered housing facilities are transferred from the orthopedic ward to the geriatric ward for approximately 1 week of physical training. Nursing home residents are generally discharged back to the nursing home due to the need of well-known surroundings because more than half of the residents are demented and at high risk of delirium [181,189]. After hospitalization, both residential groups are visited by the multidisciplinary orthogeriatric team the day after discharge and within 30 days after surgery [4]. The visits are based on the concept of "Early discharge hospital at home", which is "a service that provides active treatment by health care professionals for a condition that otherwise would require acute hospital in-patient care"

[190]. The geriatric intervention begins in the hospital and continues in the residents' homes. The visits are planned individually and the number of visits depends on the need of treatment.

At Aarhus University Hospital, the orthogeriatric teamwork has existed for 11 years. The orthopedic surgeon provides the hip fracture surgery along with the Department of Anesthesiology. In Aarhus University Hospital, the usual length of hospital stay is 2 days for nursing home residents due to their needs to return home to rehabilitation in well-known surroundings to avoid delirium, and 10 days for sheltered housing residents with hip fracture who rehabilitate in the geriatric ward. The orthopedic surgical staff cooperates with the multidisciplinary orthogeriatric team, which includes a physician (geriatrician), a nurse, and a physiotherapist who are all specialists in geriatrics. The orthogeriatric team works during daytime hours from Monday through Saturday.

Statistical considerations

All data from 'EpiData' were exported to Stata software, version 13.0 for the statistical analysis. Results were considered statistically significant at a 2-sided alpha level of 5% or less.

Power calculations

Power calculation, according to *physical recovery* during the intervention period, was based on our own data from an observational pilot study with nursing home residents after hip fracture with a Hb level between 7 mmol/L (11.3 g/dL) and 6 mmol/L (9.7 g/dL) measured within the first 2 postoperative days. A tailored intervention group who received more RBC transfusions improved the MBI sum-score by 23% after 30 days of follow-up compared to standard treatment. To obtain 85% statistical power at $p \leq 0.05$, we aimed to recruit 284 patients, which included 10% probable withdrawal.

Analyses of baseline variables

Baseline characteristics collected at enrolment were compared:

- ❖ to describe the characteristics of the trial participants, which is essential for assessing the generalizability of the results
- ❖ to demonstrate that the randomization procedure has successfully led to comparability between trial groups
- ❖ to adjust treatment effects for imbalanced variables and randomization stratification factors strongly related to the outcome

Continuous variables were compared using Student's t-test, categorical variables using Pearson's chi-squared test and Fisher's Exact test, and non-normal distributed variables using Wilcoxon's rank-sum test. The means are expressed with standard deviations (SDs) and medians with interquartile ranges (IQRs).

Comparison of RBC transfusion strategies

In this dissertation, the liberal group was calculated as the numerator and the restrictive group as the denominator (reference). Reversely, in the three added papers, the restrictive group was the numerator and the liberal group was the denominator due to the procedure in previous RCT's that aimed to reduce the use of RBC units.

Comparison of Hb concentrations days 3, 10, 17, 24, and 30 was made by using analysis of variance to test for unequal development over time, using both parallel curves and equal mean curves, followed by a Likelihood Ratio test to discriminate differences.

Primary outcome

Clinical outcomes were compared, as follows:

intention-to-treat (ITT) analyzed according to their original group assignment, whether or not this was the intervention they actually received, or if they accepted or adhered to the intervention. Alternatively, a *per protocol* (PP) analysis was made based on actual intervention received, with criteria for exclusion if inadequate adherence to the intervention was achieved [150,191,192]

- ❖ randomized study group assignment
- ❖ residential groups

Measures on MBI and CAS day 10 were categorized and compared using Pearson's chi-squared test or Fisher's exact test. Medians of NMS were compared by Wilcoxon's rank-sum test. Results were expressed with percentages or medians with IQR. Measurements on logarithm-transformed MBI sum-scores were compared in analysis-of-variance (with repeated measurement). Likelihood Ratio tests were used to test for parallel curves and equal means between the two groups. The models were checked with normal probability plots of the standardized residuals and scatter plots of the residuals versus predicted values. Furthermore, all pairwise differences between any two time points were checked with normal probability plots and for equal standard deviations and correlations (the compound symmetry model). In non-survivors, the missing physical ability values were set to zero (=no ability).

Secondary outcomes

Risk of death within two follow-up periods (30 and 90 days) was analyzed using Cox proportional hazard regression model. Each patient was followed for the same time without censoring, and only death terminated the follow-up period. Time of death was recorded by date. The assumption on proportional hazards was checked graphically using "log-log" plots of the two survival curves. Results were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs) and p-values, and illustrated by Kaplan-Meier plot.

Outcome measures for *infection* incidences during 10 days were dichotomized and presented with relative risk ratios. The number of pre- and intra-operative RBC units per patient was added to that of post-operative units to analyze a possible association between the total numbers of RBC units and risk of infection. The latter RBC units were then classified at four levels and analyzed by a logistic regression model. Post-estimation was made by Hosmer-Lemeshow test. On *infection biomarkers* equal development over time was tested, using both parallel curves and equal mean curves. As CRP data were not normally distributed a logarithmic transformation was conducted before the analysis of variance.

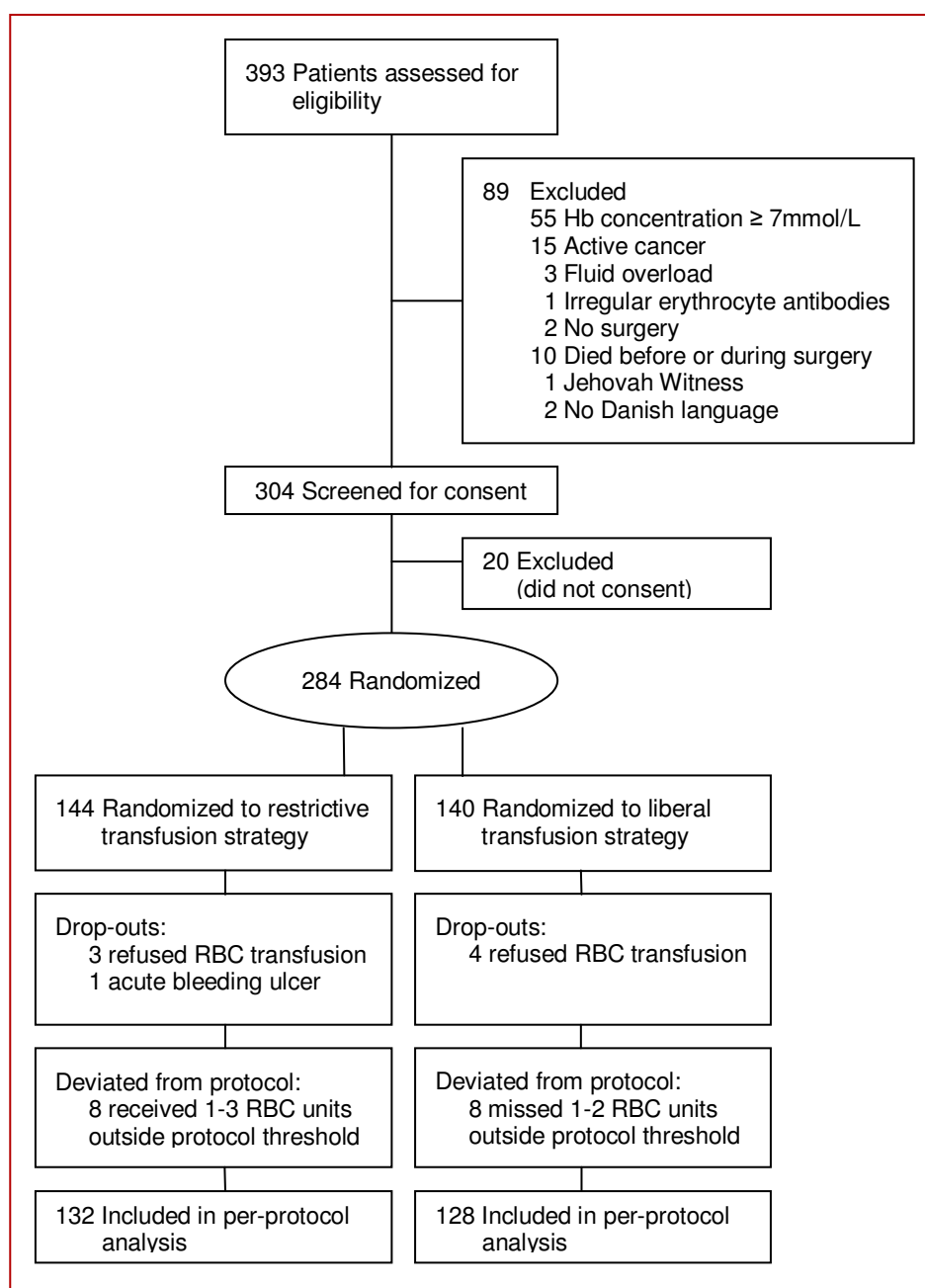
Overall Quality of Life measured by DL sum-scores day 30 and day 365 were compared by Wilcoxon rank-sum test. The association between normal distributed sum-score differences on *OQoL* (DL difference) and *ADL recovery* (MBI difference) from day 30 until 365 days after surgery was analyzed in a linear regression model. The model was checked by normal distributed residuals.

Results

Enrolment

From January 18, 2010 to June 6, 2013, we consecutively enrolled 65+ aged hip fracture patients at the Orthopedic Surgery Ward at Aarhus University Hospital (Figure 4). In total 284 patients were enrolled. Eight patients (2.8%) dropped out of the study. Seven refused RBC transfusions and 1 experienced an acute bleeding ulcer. The 8 drop-out patients did not differ from those who completed the study in terms of baseline characteristics.

Figure 4 The CONSORT diagram showing patient's flow through the study



Protocol deviation in the restrictive group involved 8 patients who received 1 to 3 additional blood units: 4 severely ill patients required additional blood as did 4 other cases after inattention to blood test results. In the liberal group, 8 patients missed one or two units of blood: 6 cases due to lack of attention to blood test results (during recovery in other departments), and 2 cases after physicians refused to prescribe RBC transfusions according to the protocol. Hence, 260 patients remained for the PP analysis.

Table 3 Baseline characteristics of 284 frail elderly hip fracture patients

Characteristics	Restrictive strategy (n=144)		Liberal strategy (n=140)		Difference in strategy groups p-value
	Nursing homes (n=89)	Sheltered housing (n=55)	Nursing homes (n=90)	Sheltered housing (n=50)	
Female gender (%)	67 (75)	41 (75)	68 (75)	38 (76)	0.89
Mean age, y (sd)	86.4 (6.65)	84.5 (7.08)	88.7 (6.25)	85.7 (7.58)	0.02
Prefracture ADL ^o (%)					
Self-sufficient	24 (27)	42 (76)	29 (32)	39 (78)	
Dependent	65 (73)	13 (24)*	61 (68)	11 (22)*	0.64
Comorbidity ^o (%)					
Low	17 (19)	16 (29)	15 (17)	24 (48)	
Moderate	53 (60)	25 (45)	59 (65)	16 (32)	
Severe	19 (21)	14 (25)	16 (18)	10 (20)*	0.51
Cardiovascular disease (%)	17 (19)	17 (31)	14 (16)	11 (22)	0.23
Dementia ^o (%)	44 (49)	2 (4)*	55 (61)	1 (2)*	0.16
Underweight ^o (%)	11 (12)	11 (20)	11 (12)	12 (24)	0.79
Prescribed medicine ^o , no (IQR)	6 (4-9)	7 (5-10)	6 (4-8)	6 (4-9)	0.45
Previous hip fracture (%)	17 (19)	7 (13)	22 (24)	11 (22)	0.15
Blood samples (sd)					
Hemoglobin (g/dL)	10.4 (1.37)	10.2 (1.17)	10.2 (1.42)	10.4 (1.45)	0.99
Erythrocyte Vol. Fraction	0.36 (0.04)	0.36 (0.04)	0.36 (0.03)	0.37 (0.04)	0.97
Sodium (mmol/L)	137.7 (4.05)	136.7 (4.57)	137.5 (4.36)	135.5 (4.65)*	0.32
Potassium (mmol/L)	4.0 (0.46)	4.0 (0.45)	4.1 (0.49)	3.9 (0.45)	0.49
Creatinine (µmol/L)	91.6 (39.8)	87.8 (38.9)	90.5 (35.2)	76.4 (26.2)*	0.27
Urea (mmol/L)	8.6 (3.48)	9.2 (4.94)	8.6 (4.28)	7.3 (2.69)*	0.13
Albumin (g/L)	34.0 (4.49)	36.0 (4.28)	34.9 (4.23)	35.8 (5.09)	0.43
Trombocytes (10 ⁹ /L)	253 (88.3)	225 (77.5)	241 (72.5)	241 (69.1)	0.79
State of delirium (%)	14 (15)	5 (9)	13 (14)	7 (14)	0.59
Waiting time for surgery, h (IQR)	17 (9-23)	18 (12-24)	15 (8-22)	16 (9-22)	0.08
Surgical treatment (%)					
Internal fixation	70 (79)	39 (71)	72 (80)	40 (80)	
Arthroplasty	17 (19)	14 (25)	16 (18)	10 (20)	
Other	2 (2)	2 (4)	2 (2)	0 (0)	0.38
Pre- and intraoperative RBC transfusions (%)	12 (13)	10 (18)	13 (14)	7 (14)	0.17

* Significant difference ($p < 0.001$) within the residents from nursing homes and sheltered housing facilities.

^o Variable used in the 'Comprehensive Geriatric Assessment – Frailty Index'¹⁵⁰

Baseline data

Baseline patient characteristics were well balanced between the transfusion groups with the exception of mean age, which was lower in the restrictive strategy group (Table 3). The data illustrated an overall majority of frail elderly with prefracture dependency in ADL, ambulation, and mobility: 57% were substantially or completely dependent on personal support, 71% was not able to walk independently (without walking aids), and 36% needed assistance for transfer from bed to chair. The nursing home residents were more frail and had a lower prefracture functional abilities than the sheltered housing residents (Table 4).

Table 4 Criteria of the Comprehensive Geriatric Assessment (CGA) Frailty Index according to residents in nursing homes or sheltered housing facilities, and the relative risk of 90-day mortality

CGA Frailty index	Residents		Difference between residents <i>p</i> -value
	Nursing home (n=179)	Sheltered housing (n=105)	
Prefracture ADL			
MBI ≥ 80 (ref)	53 (30%)	69 (65%)	
MBI < 80	126 (70%)	36 (35%)	<0.001
Comorbidity			
CCI ≤ 2 (ref)	144 (80%)	81 (77%)	
CCI > 2	35 (20%)	24 (23%)	0.51
Cognitive impairment			
MMSE ≥ 20 (ref)	32 (18%)	71 (68%)	
MMSE < 20	147 (82%)	34 (32%)	<0.001
Malnutrition			
BMI ≥ 20 and albumin ≥ 34	169 (94%)	101 (96%)	
BMI < 20 and albumin < 34	10 (6%)	4 (4%)	0.62
Multimedication			
Prescribed daily drugs ≤ 7	114 (64%)	63 (60%)	
Prescribed daily drugs > 7	65 (36%)	42 (40%)	0.54

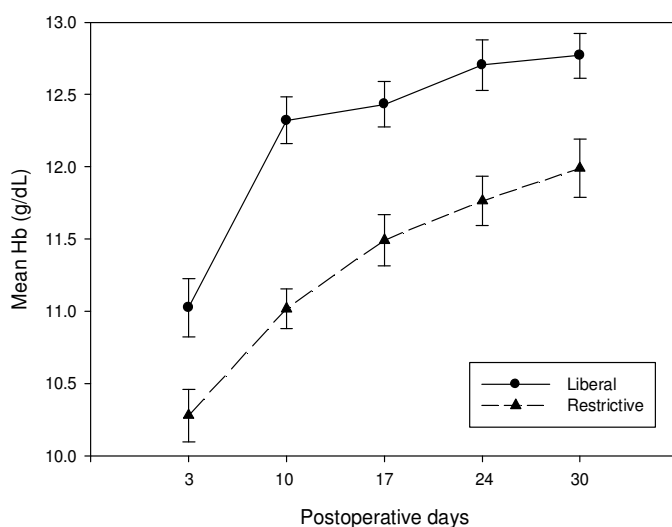


Figure 5

During the intervention period the mean hemoglobin concentrations differed significantly. Hemoglobin was measured in venous blood samples on days 3, 10, 17, 24, and 30 after hip fracture surgery. In this figure the means are presented with 95% confidence intervals.

Red Blood Cells

Figure 5 shows repeated measurements of mean Hb levels maintained at a mean of 7.01 mmol/L (95% CI: 6.99-7.04) (11.3 g/dL) for the restrictive transfusion group *versus* 7.60 mmol/L (95% CI: 7.56-7.63) (12.3 g/dL) for the liberal group. Also, Hb measurements of the two transfusion groups were tested for parallel curves ($p=0.82$) and equal means ($p<0.001$). A total of 712 RBC transfusions were administered during the study of which 73% were given during the first postoperative week. The median number of RBC units transfused per patient in the restrictive transfusion group was 1.0 (IQR 1-2) versus 3.0 (IQR 2-5) for the liberal group. In the restrictive group 35 patients (25%) received no transfusion following randomization. No complications were observed during or after RBC transfusions. The amount of RBC units is associated with transfusion strategy, Hb at admission and type of hip fracture (Table 5).

Table 5 Procedure-related variables after hip fracture surgery during the 30-day postoperative period

CGA procedures	Nursing homes			Sheltered housing		
	Restrictive strategy (n=89)	Liberal strategy (n=90)	<i>p</i> -value	Restrictive strategy (n=55)	Liberal strategy (n=50)	<i>p</i> -value
Postoperative RBC* units	1 (1 - 3)	3 (2 - 5)	<0.001	2 (1-4)	3 (2-5)	0.01
Length of hospital stay						
Median days (IQR)	2 (2-5)	2 (2-3)	0.45	11 (9-13)	10 (9-12)	0.35
Discharged from OD† to (%)						
Home	62 (70)	76 (85)		0 (0)	1 (2)	
Geriatric Department	23 (26)	12 (13)		52 (95)	47 (94)	
Another Department	2 (2)	1 (1)		3 (5)	2 (4)	
Dead	2 (2)	1 (1)	0.08	0 (0)	0 (0)	0.82
Follow-up						
Telephone consultation	4 (3-7)	5 (3-6)	0.69	3.5 (2-5)	3 (2-5)	0.81
Home visit	7 (6-8)	8 (6-9)	0.04	5 (4-5)	5 (4-6)	0.34
Fluid therapy‡	53 (60)	60 (66)	0.80	28 (51)	28 (56)	0.66
Liter	3 (2-7)	5 (2-8)	0.22	3 (1-6)	4 (2-8)	0.17
Iron therapy (tablets)	63 (71)	66 (73)	0.36	46 (84)	40 (80)	0.69
Antibiotic treatment	69 (77)	72 (80)	0.69	45 (82)	41 (82)	0.96
Osteoporosis treatment	85 (96)	88 (98)	0.26	54 (98)	48 (96)	0.32
Medication adjustment**	48 (54)	47 (52)	0.27	44 (80)	43 (86)	0.25
Time to discontinuation of strong pain killers (days)	18 (11-28)	15 (9-26)	0.73	21 (15-37)	25 (18-29)	0.36

* Red Blood Cells

† Orthopaedic Department

‡ Subcutaneous or intravenous fluid therapy

** Apart from iron, osteoporosis treatment, pain killers and laxative treatment.

Apart from the RBC transfusions, the participants received similar comprehensive geriatric assessment, treatment, and care during the 30 days of intervention (Table 6). The nursing home residents in the restrictive strategy group received less home visits from the orthogeriatric team compared to the nursing home residents in the liberal strategy group, and there was a tendency toward more residents from the restrictive group who were transferred to the geriatric ward from the orthopedic surgery ward without prolonging the length of hospital stay.

Table 6 Distribution of postoperative red blood cell units during 30 days of intervention and tested for associations with baseline variables.

	0 units (n=36)	1-2 units (n=135)	3-5 units (n=88)	>5 units (n=25)	p-value
Strategy groups (%)					
Liberal (n=140)	0 (0)	61 (44)	60 (43)	18 (13)	
Restrictive (n=144)	36 (25)	74 (51)	28 (19)	7 (5)	<0.001
Gender (%)					
Male (n=70)	10 (14)	35 (50)	18 (26)	7 (10)	
Female (n=214)	26 (12)	100 (47)	70 (33)	18 (8)	0.73
Age groups, y (%)					
65-79 (n=44)	9 (21)	22 (50)	12 (27)	1 (2)	
80-89 (n=128)	19 (15)	54 (42)	42 (33)	13 (10)	
90+ (n=112)	8 (7)	59 (53)	34 (30)	11 (10)	0.14
Residence (%)					
Nursing home (n=179)	24 (13)	89 (50)	54 (30)	12 (7)	
Sheltered housing (n=105)	12 (11)	46 (44)	34 (33)	13 (12)	0.36
Hb at admission (%)					
≥ 7 mmol/L (n=206)	32 (16)	102 (50)	63 (30)	9 (4)	
< 7 mmol/L (n=78)	4 (5)	33 (42)	25 (32)	16 (21)	<0.001
Prefracture ADL (%)					
Non-dependent (n=162)	22 (14)	77 (47)	49 (30)	14 (9)	
Dependent (n=122)	14 (11)	58 (48)	39 (32)	11 (9)	0.95
Comorbidity (%)					
Low (n=225)	27 (12)	105 (47)	72 (32)	21 (9)	
Moderate – high (n=59)	9 (15)	30 (51)	16 (27)	4 (7)	0.73
Diagnose of CVD (%)					
No (n=225)	30 (13)	104 (46)	71 (32)	20 (9)	
Yes (n=59)	6 (10)	31 (53)	17 (29)	5 (8)	0.82
Creatinine at admission (%)					
≤ 90 μmol/L (n=178)	25 (14)	80 (45)	55 (31)	18 (10)	
> 90 μmol/L (n=106)	11 (10)	55 (52)	33 (31)	7 (7)	0.51
Fracture type (%)					
Femoral neck (n=125)	24 (19)	59 (47)	38 (30)	4 (3)	
Trochanteric (n=159)	12 (8)	76 (48)	50 (31)	21 (13)	0.001
Surgical treatment (%)					
Internal fixation (n=221)	25 (11)	109 (49)	66 (30)	21 (10)	
Arthroplasty* (n=63)	11 (18)	26 (41)	22 (35)	4 (6)	0.37

*inclusive 4 patients with the Girdlestone surgery

Recovery from physical disabilities (Paper 1)

In both transfusion groups, the patient's physical abilities were statistically significantly impaired 10 days after hip fracture surgery as compared to their prefracture level ($p < 0.001$). No difference in recovery was found between the two groups according to MBI, NMS, CAS, transferring from bed to chair, or walking ability (Table 7).

Overall, the repeated measurements on MBI sum-scores, compared to prefracture level, on days 10, 30, and 90 after surgery, were similar within transfusion groups, i.e. parallel curves ($p = 0.24$) and equal means ($p = 0.27$). For nursing home residents the curves was parallel ($p = 0.36$) and the means were equal ($p = 0.32$) between transfusion groups. Likewise, for sheltered housing residents the curves was parallel ($p = 0.64$) and the means equal ($p = 0.93$) between transfusion groups (Figure 6). Similar results were found in the PP analyses.

Table 7 Intention-to-treat analyses. Physical ability scores 10 days after hip fracture surgery compared restrictive transfusion group with liberal group stratified in residents from nursing homes and sheltered housing and analyzed with Wilcoxon rank sum test.

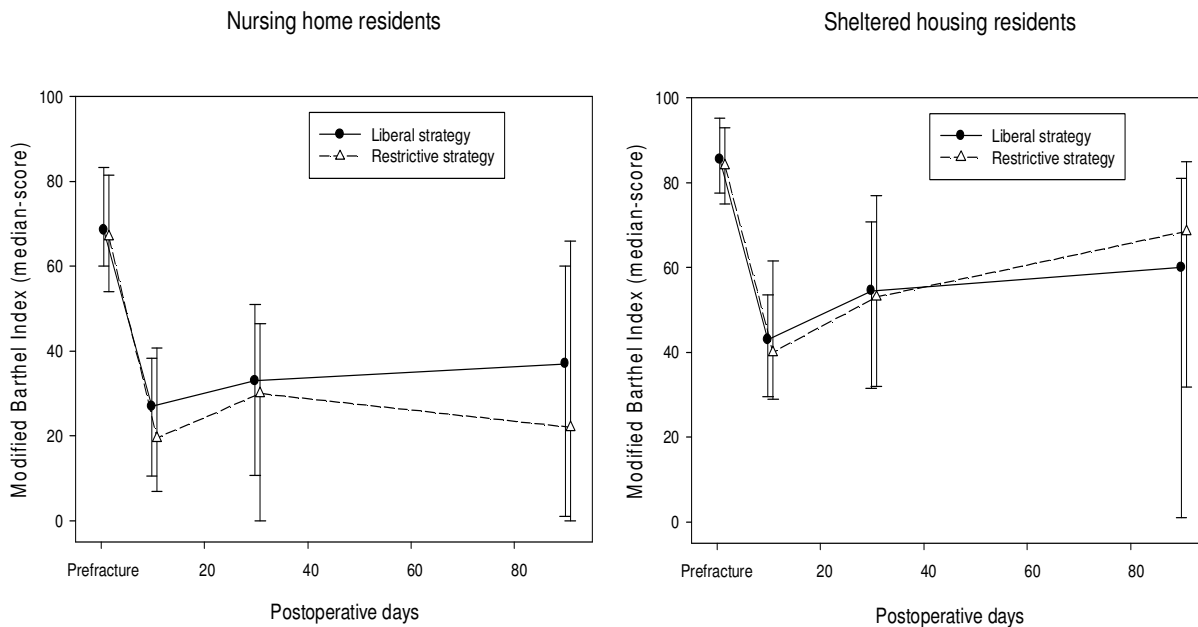
	All residents (n=284)		<i>p</i>	Nursing homes (n=179)		<i>p</i>	Sheltered housing (n=105)		<i>p</i>
	Restrictive strategy (n=144)	Liberal strategy (n=140)		Restrictive strategy (n=89)	Liberal strategy (n=90)		Restrictive strategy (n=55)	Liberal strategy (n=50)	
Physical ability 10 days after surgery									
Modified Barthel Index ¹ (%)									
Independent or moderate									
dependent	38 (26)	32 (23)		18 (20)	15 (17)		20 (36)	17 (34)	
Substantially dependent	51 (35)	58 (41)		24 (27)	33 (37)		27 (49)	25 (50)	
Completely dependent	55 (38)	50 (36)	0.56	47 (53)	42 (46)	0.37	8 (15)	8 (16)	0.96
New Mobility Score ²									
Median (IQR)	1 (0-1)	1 (0-1)	0.49	1 (0-1)	1 (0-1)	0.83	1 (1-2)	1 (1-2)	0.54
CAS Score ³ (%)									
Walking ability	19 (13)	16 (11)		4 (4)	8 (9)		16 (29)	7 (14)	
Sit-to-stand-to-sit	65 (45)	74 (53)		37 (42)	40 (44)		30 (55)	34 (68)	
Bedridden	56 (39)	50 (36)	0.53	48 (54)	42 (47)	0.24	9 (16)	9 (18)	0.17
Transfer from bed to chair (%)									
Independent	25 (17)	19 (14)		10 (11)	11 (12)		15 (27)	8 (16)	
Dependent	119 (83)	121 (86)	0.30	79 (89)	79 (88)	0.98	40 (73)	42 (84)	0.16
Walking ability (%)									
Independent	1 (1)	1 (1)		1 (1)	1 (1)		0 (0)	0 (0)	
Walking aids	25 (17)	25 (18)		7 (8)	12 (13)		18 (33)	13 (26)	
Person support	59 (41)	66 (47)		33 (37)	38 (42)		26 (47)	28 (56)	
None	59 (41)	48 (34)	0.88	48 (54)	39 (43)	0.68	11 (20)	9 (18)	0.65

¹ Modified Barthel Index -score categories: 'Independent/moderate dependent' in Activities of Daily Living (ADL) (sum-score: 100-50); 'Substantial dependent' in ADL (sum-score: 49-25); and 'Completely dependent' in ADL (sum-score: 24-0)

² New Mobility Score categories (9=best, 0=worse): 'High level' (sum-score 9-6); 'Low level' (sum-score 5-0)

³ Cumulated Ambulation Score (CAS) categories (6=best, 0=worse): 'Independence' (sum-score=6); 'Dependency' (sum-score: 5-0)

Figure 6 (Intension-to-treat) Repeated measures on physical recovery from prefracture until postoperative days 10, 30 and 90 presented with median score with interquartile ranges.



ADL-recovery (difference in MBI sum score from prefracture physical performance to 90 days after surgery) was similarly impaired in the two transfusion groups ($\beta=2.49$ (95% CI: -4.32; 9.31, $p=0.47$). In nursing home resident ADL-recovery was minus 34 points (95% CI: -94; 46) and in the sheltered housing residents minus 30 points (95% CI: -100; 10) ($p=0.25$). After 90 days, nursing home residents' MBI sum-score was lower than the sheltered housing residents' ($\beta= -21.3$ (95% CI: 13.4; -29.2, $p<0.001$). Women's ADL-recovery was better than men's ($\beta= 8.25$ (95% CI: 0.35; 16.2, $p=0.01$). Dementia, age, underweight, pain by mobilisation, fracture type, and surgical treatment were not associated with ADL-recovery. The Hb concentration in the blood after 30 days of intervention was not associated with the 30-day MBI sum score ($\beta= -3.71$ (95% CI: -9.2; 1.8, $p=0.19$).

Survival (Paper 1)

No statistically significant difference of 90-day mortality was found between the restrictive (27% died) and liberal transfusion groups (21% died) when analysed by intention-to-treat (Table 8). However, the per-protocol 30-day mortality rate was higher after restrictive transfusion. In a subgroup analysis, nursing home residents' 90-day mortality rate was statistically significantly higher after restrictive transfusions compared to liberal transfusions. Similar results were obtained with the per-protocol analyses. However, for sheltered housing residents 90-day mortality rates showed no statistically significant differences between transfusion groups (Figure 7). The main cause of death for both transfusion groups was pneumonia ($p=0.11$), (Table 9). No deaths were related to bleeding or complications to the RBC transfusions.

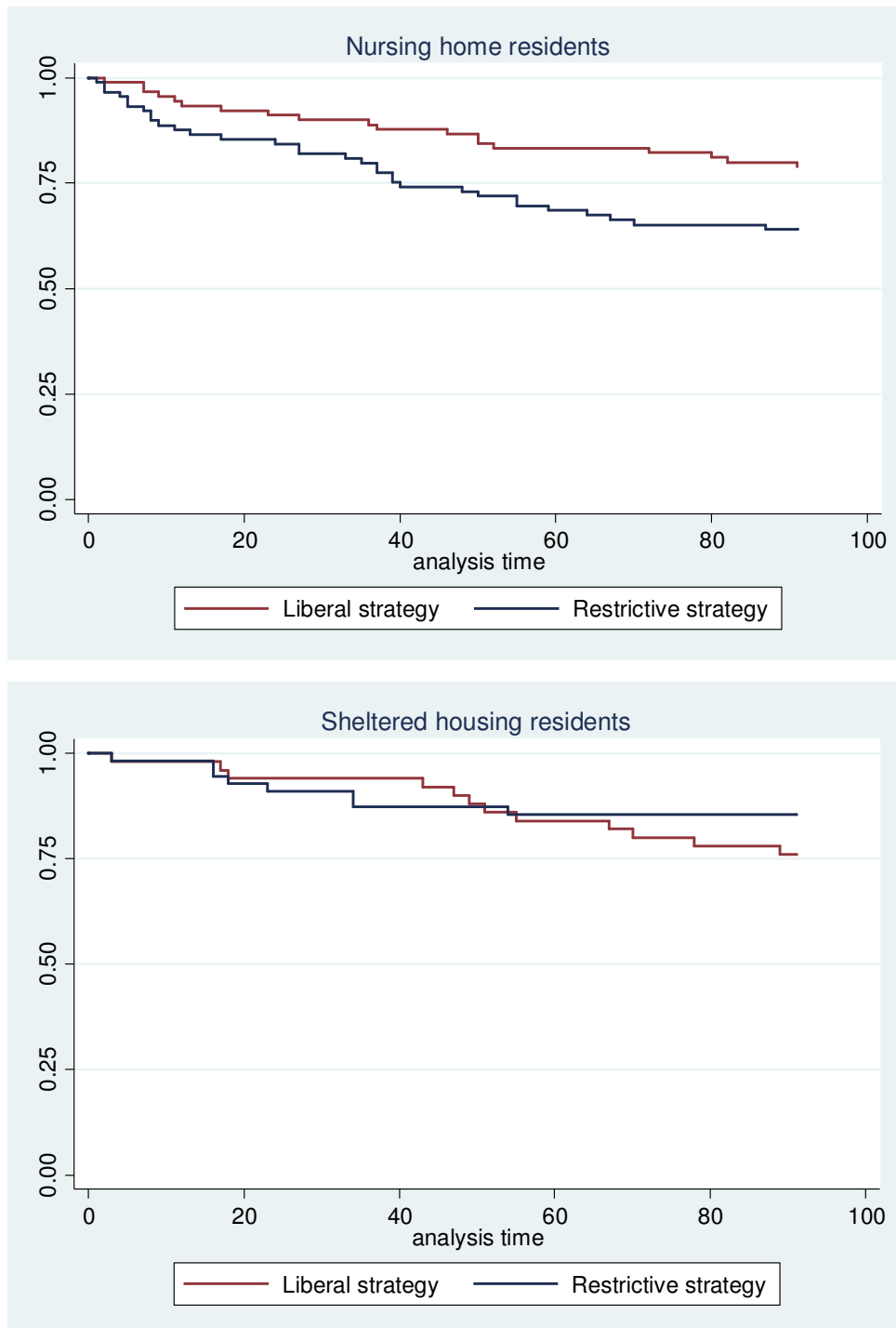
Table 8 The hazards ratio of time to death within 30 and 90 days by intention-to-treat analysis and per-protocol analysis

	30-day mortality				90-day mortality			
	Restrictive (n=144)	Liberal (n=140)	Hazard Ratio (95% CI)	<i>p</i> - value	Restrictive (n=144)	Liberal (n=140)	Hazard Ratio (95% CI)	<i>p</i> - value
Intention-to-treat								
All residents (%)	21 (14)	12 (8)	1.76 (0.86-3.58)	0.11	40 (27)	30 (21)	1.39 (0.86-2.23)	0
Nursing homes (%)	16 (18)	9 (10)	1.89 (0.83-4.29)	0.12	32 (36)	18 (20)	2.00 (1.12-3.57)	0
Sheltered (%)	5 (9)	3 (6)	1.52 (0.36-6.40)	0.56	8 (15)	12 (24)	0.60 (0.24-1.48)	0
Per-Protocol	(n=132)	(n=128)	HR (95% CI)	<i>p</i> - value	(n=132)	(n=128)	HR (95% CI)	<i>p</i> - value
All residents (%)	21 (16)	9 (7)	2.36 (1.08-5.16)	0.03	35 (27)	26 (20)	1.41 (0.84-2.34)	0
Nursing homes (%)	16 (20)	8 (10)	2.15 (0.92-5.03)	0.07	28 (35)	17 (20)	1.85 (1.01-3.38)	0
Sheltered (%)	5 (10)	1 (2)	4.58 (0.53-39.2)	0.16	7 (13)	9 (19)	0.72 (0.27-1.95)	0

Table 9 Causes of deaths during 90 postoperative days in frail elderly hip fracture patients.

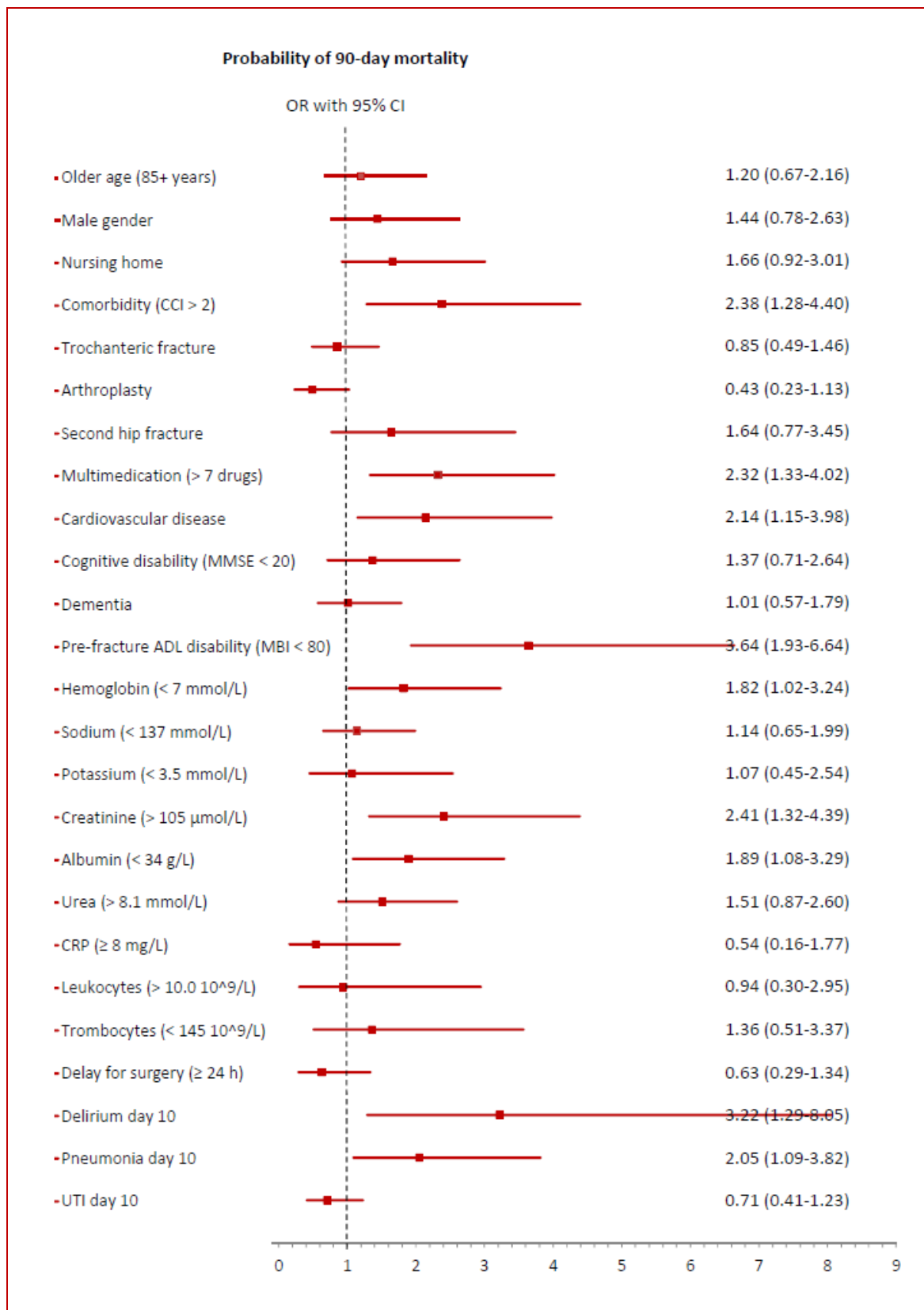
Causes of deaths	Deaths		
	Liberal strategy group (n=30)	Restrictive strategy group (n=40)	<i>p</i> -value
Pneumonia (%)	8 (27)	18 (44)	0.11
Heart failure (%)	3 (9)	11 (28)	0.07
Sepsis (%)	3 (9)	5 (11)	0.74
Dementia (%)	3 (9)	4 (10)	0.98
Stroke (%)	8 (27)	2 (7)	0.02
Liver failure (%)	4 (13)	0 (0)	-

Figure 7 The plots show the Kaplan-Meier estimates of 90-day survival rates after hip fracture in residents from nursing homes and sheltered housing facilities by Intention-to-treat analysis.



Among the baseline variables biomarkers at admission: severe comorbidity, multimедication, CVD, ADL disabilities, low hemoglobin, high creatinine, and low albumin were independently associated with 90-day mortality (Figure 8). Pneumonia and delirium assessed 10 days after surgery were also associated with 90-day mortality when adjusted for transfusion strategy.

Figure 8 The odds ratio (small red boxes) with 95% confidence intervals (horizontal lines) for the outcome measure of death by day 90 among all the patients, as assessed by logistic regression analysis with adjustment of RBC transfusion strategy. The size of each red box is compared to the corresponding subgroup in all the baseline variables and potential predictors of mortality: delirium, pneumonia, and UTI 10 days after surgery.



Infection risk (Paper 2)

The overall risk of postoperative infection was similar for the two transfusion groups. No incidence difference was found among the types of treatment-required infection incurred by residents of either nursing homes or sheltered housing (Table 10).

Table 10 (Intention-to-treat) Distribution of postoperative infections after restrictive or liberal RBC transfusion thresholds within 10 days after hip fracture surgery and presented as relative risk ratios with 95% confidence intervals (CI).

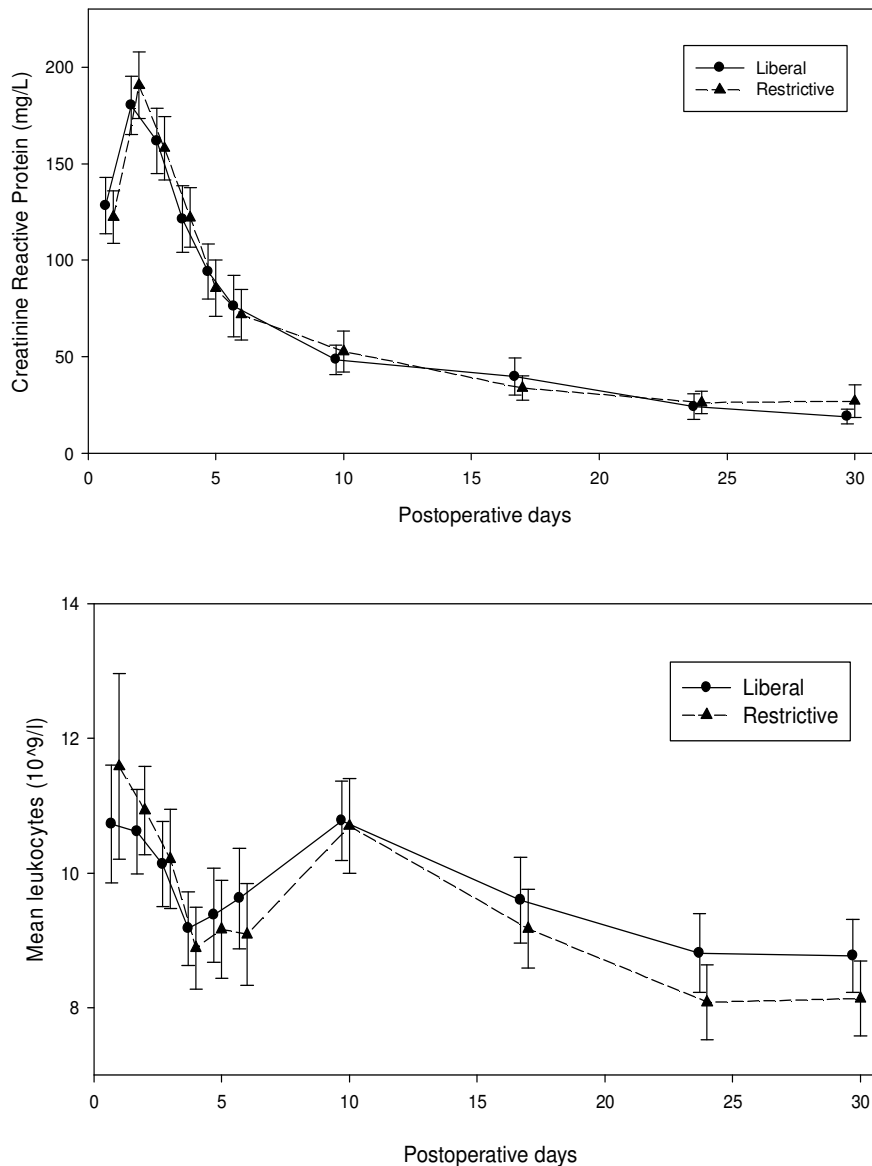
10-day outcomes	Nursing home residents			Sheltered housing residents		
	Restrictive n=89	Liberal n=90	Risk Ratio (95% CI)	Restrictive n=55	Liberal n=50	Risk Ratio (95% CI)
Incidence of one or more infections (%)						
No	25 (28)	34 (38)	1.00 (reference)	15 (27)	13 (26)	1.00 (reference)
Yes	64 (72)	56 (62)	1.15 (0.94-1.42)	40 (73)	37 (74)	0.98 (0.78-1.2)
Pneumonia (%)						
No	71 (80)	72 (80)	1.00 (reference)	43 (78)	40 (80)	1.00 (reference)
Yes	18 (20)	18 (20)	1.01 (0.56-1.81)	12 (22)	10 (20)	1.09 (0.51-2.3)
UTI* (%)						
No	43 (48)	53 (59)	1.00 (reference)	25 (45)	25 (50)	1.00 (reference)
Yes	46 (52)	37 (41)	1.25 (0.91-1.72)	30 (55)	25 (50)	1.09 (0.76-1.5)
Other infections (%)						
No	87 (98)	87 (97)	1.00 (reference)	55 (100)	50 (100)	1.00 (reference)
Yes	2 (2)	3 (3)	0.67 (0.11-3.94)	0	0	-

* Urinary Tract Infection

In total, 69% of the patients in the study experienced at least one infection during the 10 days after hip fracture surgery. The incidence of pneumonia within 10 postoperative days was similar among both transfusion groups: restrictive 21% *versus* liberal 20% ($p=0.86$), and was independent on type of residence. Likewise, the UTI rate within 10 postoperative days was similar among both transfusion groups: restrictive 53% *versus* liberal 44% ($p=0.15$). There was no significant difference between other infection (surgical wound infection, erysipelas, sepsis, pyelonephritis, and infections without focus) rates: restrictive 1.3% *versus* liberal 2.1% ($p=0.63$). Similar results were found with the per-protocol analysis.

The mean curves of leukocyte counts of both groups were parallel over the 30 days ($p=0.17$) and mean counts were equal ($p=0.62$). The same situation applied to repeated measurements of CRP concentrations. The test showed parallel curves ($p=0.94$) and equal means within the two transfusion groups ($p=0.86$) (Figure 9).

Figure 9 Mean leukocytes and C-reactive protein (CRP) concentrations with 95% confidence intervals for repeated measurements during 30 days of intervention with restrictive and liberal RBC transfusions.



RBC transfusions given pre- an intra-operatively were administered equally in the groups by 16% in the restrictive transfusion group *versus* 14% in the liberal group ($p=0.58$). The numbers of these transfusions combined with the transfusions given during the intervention period showed that the number of RBC units transfused were not associated with higher infection probabilities (Table 3). The incidence of infection was similar for both transfused patients and non-transfused patients ($p= 0.29$).

Pneumonia within 10 days was associated with 90-day mortality (RR 1.73; 95% CI: 1.09-2.75, $p=0.02$) and male gender (RR 1.86; 95% CI: 1.18-2.95, $p=0.008$). UTI within 10 days was not associated with 90-day mortality (RR 0.85; 95% CI: 0.63-1.15, $p=0.27$), but

was associated with female gender (RR 1.47; 95% CI: 1.05-2.07, $p=0.01$). Infections in total were not attributable to the surgical procedures, i.e. arthroplasty *versus* internal fixation (RR 0.89 (95% CI: 0.72-1.09, $p=0.25$).

Table 11 The probability of infections related to the number of intra- and postoperative red blood cell units regardless randomization in 284 frail elderly hip fracture patients analysed by a logistic regression model and presented as odds ratios with 95% confidence intervals (CI).

	Red blood cell units				Odds Ratio [†] (95% CI)
	0 n=35	1-2 n=121	3-5 n=95	>5 n=33	
1-10 days after surgery					
Pneumonia (%)	8 (23)	27 (22)	19 (20)	4 (12)	0.92 (0.80-1.05)
Urinary tract infection (%)	18 (51)	59 (49)	47 (49)	14 (42)	0.97 (0.88-1.08)
Other infections (%)	0	1 (0.8)	4 (4)	0	1.17 (0.87-1.61)

[†] The odds ratio of the outcomes compared to the ordered exposure variable (blood units per patient)

Quality of Life (Paper 3)

Baseline characteristics

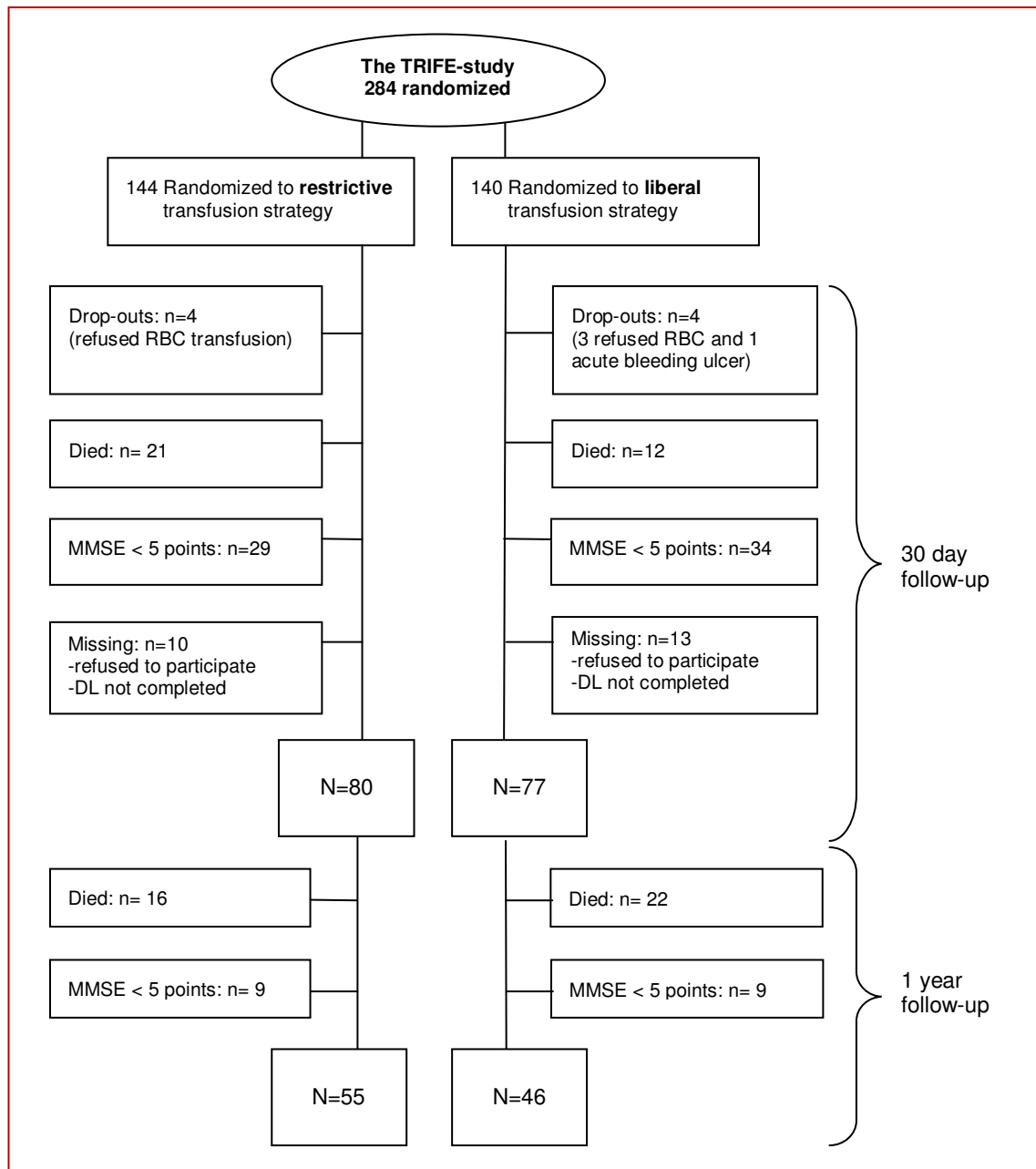
Figure 1 illustrates patient selection from the TRIFE study population. Excluded patients who had died, dropped out, or yielded MMSE sum-scores <5 points, left 180 patients (63%) for the study of OQoL. On day 30, DL sum-score data were missing for 23 patients. The ‘non-completers’ were more frequently nursing home residents with more severe comorbidities and, in terms of ADL, more dependence. Table 1 presents baseline variables for the study population in paper 3. In this population a total of 467 RBC units were administered of which 76% were given within the first 5 days after surgery. Median RBC units transfused per resident in the restrictive group were 1.5 (IQR 1-2.5) and 3.0 (IQR 2-4) for the liberal group ($p<0.001$). Restrictive group patients (24%, $n=19$) required no RBC transfusions during the intervention period since their Hb concentrations did not decrease below the protocol limit of 9.7 g/dL, whereas all patients in the liberal group received at least one transfusion. Repeated Hb measurements yielded a mean of 11.3 g/dL (95% CI, 11.2-11.5) for the restrictive transfusion group versus 12.3 g/dL (95% CI, 12.2-12.5) for the liberal group ($p<0.001$).

OQoL in the two transfusion strategy groups

Among all 157 residents no Overall Quality of Life difference assessed by median Depression List (DL) sum-scores was observed between the two RBC transfusion groups 30

days after hip fracture surgery ($p=0.16$). The DL questionnaire yielded data on 101 residents one year after surgery. Median DL sum-scores showed no difference between the RBC transfusion groups at one year ($p=0.75$) (Figure 2). Increases of DL sum-scores from day 30 to 1-year were 0.78 point (± 4.30) for the restrictive group versus 1.84 point (± 4.23) for the liberal group ($\beta=1.06$ [95% CI: -0.62; 2.76] $p=0.21$).

Figure 10 Flowchart of participants available for Overall Quality of Life measurement



ADL recovery in the two transfusion groups

In the restrictive group the median Modified Barthel Index (MBI) sum-score at one year was 76 (IQR: 48-86). The MBI sum-score increased by 9.18 points (± 16.1) from day 30 until 1 year after surgery. In the liberal group the median MBI sum-score at 1 year was 78 (IQR: 61-86) and the MBI sum-score increased by 16.0 points (± 16.5), from day 30 until 1 year after surgery, which was statistically significantly greater than the restrictive group ($\beta=6.86$ [95% CI: 0.41; 13.3] $p=0.03$).

OQoL and ADL-recovery for both groups combined

Depression List sum-scores assessing OQoL increased for the combined transfusion groups by 1.27 point (95% CI: 0.42; 2.11, $p=0.003$), from day 30 until 1 year after surgery. On day 30, patients scored their highest points (i.e. lowest OQoL) on *physical function items*: appetite, fatigue, feeling old, liveliness, helplessness and weakness; whereas *emotional and social items*: life-satisfaction, sleep, health, friends, visits, mood, boredom, and life expectations improved. State of frailty was significantly associated with lower 30-day OQoL ($p=0.03$), but at 1 year ($p=0.65$).

The MBI sum-score mean increased by 12.3 points (95% CI: 9.04-15.6, $p<0.001$) from 57.2 points (± 22.0) on day 30 after surgery to 69.5 points (± 23.9) at 1 year. The increases of DL and MBI sum-scores were independently associated $\beta= -0.06$ (95% CI: -0.11; -0.01) $p=0.02$. Pre-fracture physical abilities (14 days before the fracture occurred), were not achieved 1 year later. The 1-year MBI sum-score was impaired by 10.8 points (95% CI: 7.38; 14.2, $p<0.001$) (Figure 11).

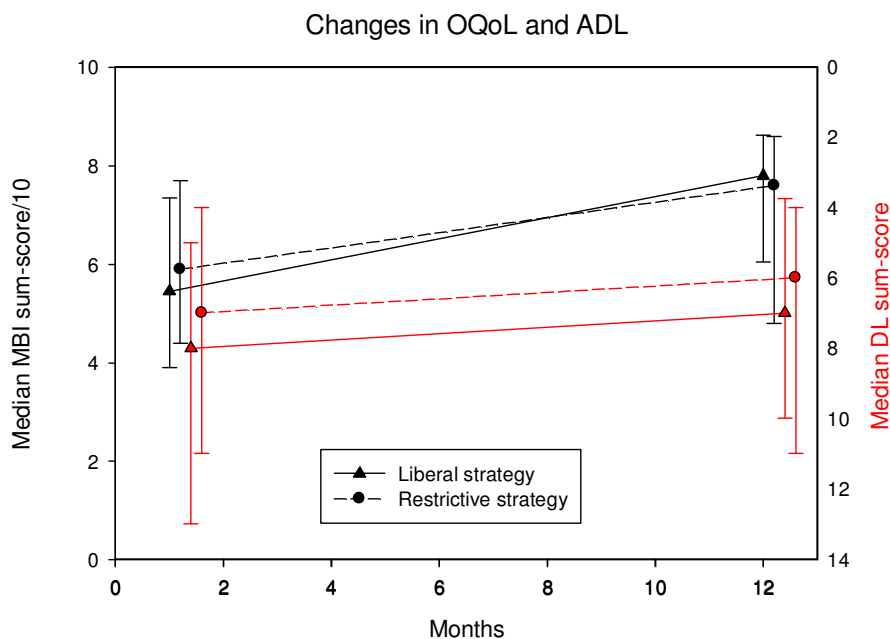


Figure 11 Change from day 30 to 1 year after hip fracture surgery in Overall Quality of Life measured by Depression List (DL) and ADL measured by Modified Barthel Index (MBI) sum-score medians with inter-quartile range. Best DL sum-score is 0. Best MBI sum-score is 100:10.

Table 12 gives an overview of frailty items according to all outcomes after 30 days intervention of RBC transfusions.

Table 12 All clinical outcomes after 30 days of intervention according to CGA Frailty Index.

Frailty criterias	30-day outcomes			
	Physical performance* points (95% CI)	Mortality OR (95% CI)	Infection OR (95% CI)	Overall Quality of Life ^ points (95% CI)
Overall frailty				
No	1.00	1.00	1.00	1.00
Yes	-21 (-31; -10)	4.34 (0.57; 33)	1.07 (0.87; 1.30)	2.18 (0.05; 4.33)
Prefracture ADL				
MBI ≥ 80 (ref)	1.00	1.00	1.00	1.00
MBI < 80	-30 (-35; -25)	6.43 (2.19; 18.8)	1.56 (0.84; 2.87)	0.70 (0.04; 11.5)
Comorbidity				
CCI ≤ 2 (ref)	1.00	1.00	1.00	1.00
CCI > 2	-4.11 (-12.1; 3.86)	2.48 (1.14; 5.39)	2.14 (0.86; 5.31)	-1.81 (-3.94; 0.32)
Cognitive impairment				
MMSE ≥ 20 (ref)	1.00	1.00	1.00	1.00
MMSE < 20	-22 (-28; -16)	2.77 (0.77; 9.90)	0.97 (0.50; 1.86)	1.39 (-2.12; 1.32)
Malnutrition				
BMI ≥ 20 and albumin ≥ 34 (ref)	1.00	1.00	1.00	1.00
BMI < 20 and albumin < 34	-1.16 (-16; 14)	1.28 (0.27; 6.01)	2.88 (0.36; 23)	1.42 (-4.08; 6.93)
Multimedication				
Prescribed daily drugs ≤ 7 (ref)	1.00	1.00	1.00	1.00
Prescribed daily drugs > 7	-1.90 (-8.60; 4.79)	2.51 (1.20; 5.25)	1.51 (0.78; 2.92)	-1.59 (3.37; 0.19)

*Modified Barthel Index sum score

^ n=157

Discussion

In this PhD project we included 284 elderly patients after hip fracture surgery. We compared a restrictive strategy (target: Hb 6 mmol/L; 9.7 g/dL) with a liberal RBC transfusion strategy (target: Hb 7 mmol/L; 11.3 g/dL). Randomization was stratified according to gender and type of residence: nursing homes and sheltered housing facilities. The nursing home residents were the frailest elderly. We found that survival increased in the nursing home residents with higher Hb concentrations. We assume that it was the frailest elderly in the liberal transfusion group who survived and the frailest elderly in the restrictive group who died. Survival occurred without impairing recovery from physical disabilities and reducing Overall Quality of Life. The higher number of RBC transfusions did not cause more treatment-requiring infections. After 1 year, physical abilities improved in the survivors without very severe cognitive disabilities as a result of the liberal transfusion strategy. Both physical ability and OQoL increased one year after hip fracture from 30 days after surgery until 1 year after and were associated.

Comparison with existing literature

Meeting the demand for RBC resources is one of the most difficult challenges for healthcare providers. Since we initiated this project in frail elderly hip fracture patients, there has been much focus on minimizing the use of blood, thus a new and even more restrictive recommendation was published by The Danish Health and Medicine Authority based on the existing evidence-based literature. The use of RBC transfusions is considered when the Hb thresholds are:

- ❖ < 4.3 mmol/L (7 g/dL) in circulation stabile patients without heart disease
- ❖ < 5.0 mmol/L (8 g/dL) in patients with chronic heart disease
- ❖ < 5.6 mmol/L (9 g/dL) in patients with acute ischemic syndrome or life-threatening bleeding

This recommendation is considered applicable for all patient groups – also the frail elderly with hip fracture.

Many observational studies have compared risk factors in transfused and non-transfused patient without taking into account the frailty aspect, thereby confounding the results. Likewise, several experimental studies have compared restrictive RBC transfusion strategies with liberal strategies in many different patient populations, with different Hb thresholds and various lengths of intervention periods, thereby making it difficult to accurately compare the results. These studies aimed at reducing the use of RBC units without

harming the patients. In our study, we wanted to see whether we could improve patient outcome by a more liberal blood transfusion strategy.

The FOCUS study with 2,016 high-risk elderly hip fracture patients (mean age 81.6 years) had either clinical evidence of or risk factors for cardiovascular disease, of whom 10% were nursing home residents [137]. Unfortunately, the researchers did not apply a subgroup analysis for only the nursing home residents. Our study investigated the RBC transfusion effects on frail elderly hip fracture patients with a higher mean age (86.7 years), high rate of comorbidity and dementia, and impaired physical ability. Interestingly, the results on infection and mortality in the FOCUS study might have been stratified by residence making it possible to examine whether the outcomes of the nursing home residents (N=214) were consistent with our findings. However, the FOCUS study's restrictive Hb target was 1.7 g/dL lower than our restrictive Hb target and their liberal target was 1.3 g/dL lower than our liberal Hb target. Therefore they may not have found any difference in patient outcomes between the two Hb thresholds, and they conclude that Hb levels as low as 5 mmol/L (8 g/dL) are reasonable in hip fracture patient undergone surgery in the absence of symptoms of anemia.

Our intervention period regarding RBC transfusions was longer than several previous studies because we took cognizance of the findings of Foss et al, that blood loss after surgery for hip fracture is up to six times that observed during the surgical procedure [193], and gastrointestinal bleeding or ulceration is a frequent complication in the elderly hip fracture patients and independently associated with increased blood loss [55]. Twenty-seven percent of our patients needed proton pump inhibitors within 30 days after surgery. Therefore a longer follow-up period was needed to capture reduction in Hb after surgery.

Recovery from physical disabilities

Our RCT was the first to examine the effect of Hb level on rehabilitation solely in the frailest hip fracture patients with acute anemia. A large proportion of the residents had poor physical performance already before the trauma. The potential for optimal recovery was thus unfavorable because poor prefracture physical functional capacity is associated with impaired recovery [24,45,60]. Only very few of our participants reached their prefracture physical ability within 3 months of follow-up. The outcome regarding physical ability after 1 year, where recovery was expected to peak [58], might have been underestimated due to the high 1-year mortality rate of 45% in the nursing home residents. However, we found that ADL recovery was increased by the liberal transfusion strategy.

Half of the residents in each RBC transfusion group were prefracture anemic as defined according to WHO [194]. However, it was unclear whether this anemia was chronic

or due to the present hip fracture. Nonetheless, several studies found an association between chronic anemia and decreased physical ability due to reduced muscles strength in the elderly [25]. In that respect, both the poor prefracture physical ability and (chronic) anemia were two of many factors affecting the functional prognosis. Furthermore, cognitive impairments, comorbidity, and high age seem to negatively influence the physical functional outcome [69].

In previous studies, the Hb targets of RBC transfusion differed within a range of 7-9 g/dL (4.3-5.6 mmol/L) as the restrictive strategy, and within a range of 9-10 g/dL (5.6-6.2 mmol/L) as the liberal strategy. Carson and colleagues did not find better walking abilities in association with a higher Hb level in high-risk hip fracture patients who walked without human assistance prior to hip fracture compared to a restrictive threshold. However, their restrictive strategy group received RBC transfusion if signs of anemia were chest pain, congestive heart failure, and unexplained tachycardia, or hypotension unresponsive to fluid replacement [137]. Foss and colleagues also did not find a positive association between Hb level and ambulation [72]. As in our study, the ranges between the RBC transfusion strategy targets might not have been large enough to show any improvements. Instead, our restrictive strategy might have been as low as the new recommendation from the Danish Health and Medicine Authority (page 54).

Mortality

Several RCTs in various patient populations have already concluded that RBC stocks can be saved without increasing short-term mortality. Carson and his colleagues concluded in their meta-analysis from 2012 of 11 RCTs that 30-day mortality is not affected in relation to the RBC transfusion strategies in varying populations [10]. The same was true for 60-day mortality, which was combined in three RCTs. A restrictive strategy is at least as effective as a liberal strategy. In *hip fracture patients* (FOCUS study), Carson et al. in a study in which 10% were nursing home residents found no short-term mortality differences between liberal and restrictive RBC transfusion strategies [137]. The same conclusion was achieved in a recent Scandinavian multicenter RCT in *patients with septic shock* [140]. However, Salpeter et al concluded in their meta-analysis from 2014 on the basis of three RCTs in *pediatric intensive care patients and adults with critical illness or bleeding*, that mortality was reduced by restricted blood transfusions less than 4.3 mmol/L (7 g/dL) compared to a more liberal threshold [152].

Hébert et al. found significantly lower mortality in intensive-care units when RBC transfusions were administered to *patients with coronary artery disease* [37]. Also, Pinheiro de Almeida et al. found that a liberal RBC transfusion threshold of 5.6 mmol/L (9 g/dL) in

surgical oncologic patients was associated with fewer complications and reduced mortality compared to a restrictive strategy of 4.3 mmol/L (7 g/dL). These patients may be more susceptible to altered oxygen delivery and impaired tissue oxygenation during the postoperative period, which may be similar to the situation in our patients. The main cause of mortality in the oncologic patients was multiple organ failure as a result of septic shock. Also, Park et al. found in *patients with septic shock and severe sepsis* that the risk of 28-day mortality was lower in those patients who received RBC transfusion after adjustment for possible confounding factors in a propensity matched cohort study design [124]. In *patients with symptomatic coronary artery disease*, a recent RCT pilot study showed that deaths were less frequent in the liberal transfusion group compared to the restrictive group (1.8% versus 13%) [146]. Even though only 110 patients were included and the study was underpowered, it seems that higher Hb, delivering needed oxygen to a vulnerable heart muscle in patients with coronary diseases, is life-saving.

The Hb targets for RBC transfusion may be different in patients with gastrointestinal hemorrhage, in CVD patient, or even in frail elderly hip fracture patients. The various patient populations, e.g. children and elderly, cannot be pooled, but the disease and state of frailty must be taken into account. Furthermore, the very low liberal RBC transfusion strategy in many studies may eliminate the effect of life-saving outcomes.

CGA was conducted to the same extend in the liberal and restrictive groups. If CGA and the RBC transfusion strategies were not combined, we might not have been able to find the same significant results. In some of the orthogeriatric models, there are effects concerning better functional recovery, shorter length of hospital stay, fewer complications and reduced mortality [88,174,178].

The predictors of 90-day mortality after hip fracture are very similar to the constructs of frailty measured by CGA Frailty Index [150]. Surgery delay did almost not exist in our hospital. The time from admission to surgery was 16 hours compared to other studies with 3.5 days to surgery, even though it is well-known that surgery delay is associated with mortality and risk of complications [52,96,195], especially in the frail elderly with prefracture functional impairment. In the literature, postoperative anemia is associated with delirium and nosocomial infection in surgical hip fracture patients [30,49]. Prolonged delirium and pneumonia are both associated with death [35,53,95], as we found in our study. Cognitive impairment and/or age ≥ 85 years is associated with higher incidences of delirium and mortality [35,45,50,110]. However, these predictors of 90-day mortality need to be further investigated in future studies.

Our 90-day mortality rate was similar to rates reported in other studies involving nursing home residents with hip fracture [3]. The 90-day mortality rate in our nursing home residents in the restrictive transfusion group was rather high (36%), and higher than the 27% we previously observed. Berry et al. found that the overall 90-day mortality rate of nursing home residents admitted to long-term care in a rehabilitation center with geriatric specialists (Boston, USA) was 21% after hip fracture surgery which was similar to the 20% in our liberal strategy group [33-35]. However, we are unable to make further comparisons, since no data was available in the Boston study on RBC transfusion strategy for this group of nursing home residents.

We found that stroke was a more frequent cause of death in the liberal transfusion group, whereas heart failure was more frequent with borderline significance in the restrictive transfusion group. These possible relationships need to be further investigated because information was obtained from death certificates only and not from autopsies. However, when the cardiovascular diseases were combined, no difference was found in mortality.

We agree with Carson that outcomes such as mortality, myocardial infarction, and function should be considered in the overall risk-benefit analysis of RBC transfusion [196,197]: “Every time we think of a patient with different diagnoses and comorbid illnesses, we need to think of a safe hemoglobin concentration as a target to administer blood” [198].

Infection risk

Available observational studies support the hypothesis of an increased risk of postoperative infections in recipients of RBC transfusions compared with patients who have not been transfused. Some investigators excluded certain types of infections such as UTI from the definition of postoperative infections although only UTI is found to be statistically significant in elderly transfused hip fracture patients after adjustment of confounders, in comparison to patient not transfused [199]. The immunomodulatory effects of RBC transfusions might not be related to the blood itself, but rather to other unmeasured clinical variables. Some studies used leukodepleted RBC units as we did. The leukocyte component of transfused blood might be related to development of acute lung injury, immunosuppressive effects, postoperative infections, and systemic inflammatory response syndrome [141]. A meta-analysis demonstrated that postoperative infections decreased in patients transfused with leukoreduced RBCs [200].

The FOCUS study found no association with serious adverse events (e.g., wound infection, myocardial infarction, and pneumonia) [137]. Rohde et al. reported in the first publication release of their meta-analysis a reduced risk of health care-associated infection

with a restrictive RBC transfusion strategy (Hb threshold range: 4-6 mmol/L) compared to a liberal strategy (Hb threshold range: 5.6-7mmol/L) [143]. They had included preliminary results from our TRIFE study, unfortunately using our hazard ratio with inverse outcome. Another limit of this meta-analysis was that the included trials reported various infectious outcomes. In some trials, all infections are listed, whereas in others, only report specific types of infections are listed. When Rohde et al. re-analyzed the data, health care-associated infections were no longer associated with a restrictive RBC transfusion strategy compared to a liberal strategy [201].

Anemia is known to be associated with an increased risk of nosocomial infections [49]. Postoperative Hb concentrations <10 g/dL are associated with complications such as UTI and pneumonia [45], and pneumonia has been linked to death [35]. Frailty, too, can increase morbidity. Frail elderly patients have impaired immune responses [149,151] and frequently succumb to infections, as shown in our study. Furthermore, the high infection rate may be related to our daily screening. Several studies only count the outcome of infection during hospitalization. The FOCUS study measured infections from randomization (within the first 3 days after surgery) to discharge (4 days in USA and 12 days in Canada) [137]. After discharge, infections were obtained by telephone follow-up from patients or their relatives, with high risk of recall bias.

Blood management factors may also account for the diverse results of previous years, e.g. RBC units with leukocyte depletion, RBC transfusions with stored rather than fresh blood, and different RBC thresholds as targets for transfusion. In our study we did not register the age of the RBC products. Depending on the stock of blood, the oldest blood was delivered from the blood bank (max. stored 5 weeks). However, the risk of receiving the oldest blood is distributed equally in the two study groups, and findings in a recent RCT showed no association between mortality and age of blood units [126].

The leukocytes counts in our serial blood samples showed a minor trend towards non-parallel curves over time, i.e. liberal transfusion patients showed higher mean leukocyte concentrations toward the end of the intervention period. An explanation could be that more patients survived in the liberal group, hence in the ITT analysis more survivors became exposed to infections during the intervention period thus increasing the leukocyte counts. Alternatively, leukocytes may have accumulated from the additional RBC units transfused.

Quality of Life and ADL recovery

Quality of Life (QoL) assessment has become increasingly common to supplement the objective measurements of health in clinical research, and is important in assessing

effectiveness of interventions or making treatment decisions [202]. If we prevent short-term mortality in the most frail nursing home residents after hip fracture surgery with a liberal transfusion strategy, did this mean that we were able to keep their OQoL at an acceptable level despite frailty. Obviously, we could not measure OQoL in the residents who died and in residents with a MMSE < 5 points; however, OQoL was not poorer in the liberal group compared to the survivors in the restrictive group.

Whereas Conlon et al. found that higher Hb levels at discharge correlated with a positive change of QoL scores from pre-fracture up to 60 days after surgery in elderly hip arthroplasty patients [84], we found no similar association between RBC transfusion strategies and OQoL. The observation that more nursing home residents survived in the liberal transfusion group compared to the restrictive transfusion group may have influenced OQoL measurement negatively, since we assumed that patients given liberal transfusions were the frailest residents who would have died with a restrictive strategy. Consequently, frailty was more prevalent in the liberal transfusion group. Also, we found that frailty was associated with lower OQoL. Hence, we were unable to demonstrate an association between transfusion strategies and OQoL.

Studies in older patients have demonstrated associations between chronic anemia and health-related QoL (HRQoL) [77,15,32]. In chronically anemic elderly patients, HRQoL is diminished in nursing home residents compared to the general population [76]. Also, Lucca et al. found that frail nursing home residents reported a lower HRQoL than non-frail residents [77] - as we found in our study. Elderly long-term care residents with values of Hb < 6.2 mmol/L (10 g/L) have a significantly lower HRQoL than residents with Hb > 8.1 mmol/L (13 g/dL) [15,31,32]. It is questionable, however, whether the impact of acute and chronic anemias on OQoL are comparable. Acute anemia is associated with blood loss, e.g. in relation to hip fracture surgery, whereas chronic anemia is prevalent in older patients due to frailty and comorbidities.

Recovery of ADL from 30 days until 1 year after hip fracture surgery was increased by liberal transfusions, as compared to the restrictive strategy. However, this applied only to surviving patients who were able to complete the DL questionnaire. Previous studies indicated that patients with anemia show a lower rate of recovery from physical disability compared to those with normal Hb levels [22,23].

At the 1-year follow-up most patients of both groups did not regain their ADL-levels prior to fracture. Ortiz-Alonso et al. found similarly that 1 year after hip fracture, almost 50% of patients did not regain their prefracture ADL status, and the most elderly (≥ 85 years) required an extended time to recover, owing to slowly returning to homeostasis or acute

medical problems [58]. Beaupre et al. found, too, that functional physical status decreased for nursing home residents during the 12 months after hip fracture [59].

OQoL progress and ADL recovery, from 30 days until 1 year, were independently associated. Studies in elderly hip fracture patients found, too, that physical measurements are highly correlated with HRQoL [85], and that patients with good mobility produced significantly better QoL scores than those with impaired mobility [86]. The relationship between OQoL and ADL recovery scores indicates that frail elderly need optimal rehabilitation both in hospital and after discharge to improve their OQoL, even though their potential for OQoL improvement remains rather low. Home rehabilitation programs have been shown to re-establish the physical function of elderly more rapidly after hip fracture surgery, with long-term positive effects on both ADL-independence and HRQoL [203].

Hip fracture has a long-term impact on HRQoL and is a strong predictor of worsened physical health [204]. A Short Form-36 (SF-36) is used by most studies reporting HRQoL and Hb levels [85]. Most of our patients were frail at baseline, leading to very low physical capacity after hip fracture surgery. With regard to HRQoL, nursing home residents in general score worse on physical functioning and best on social functioning [76], as we also found in our subscale analyses.

Generalizability and frailty

Patient frailty has not been the issue for the previous RCTs examining RBC transfusion strategies, despite the fact that frailty among nursing home residents is well-known, and anemia in nursing homes residents is related to 90-day mortality [35]. Nursing home residents generally require continual care and generally manifest other significant deficiencies in, e.g. ADL and cognition [40,205,206]. Previously we have reported that 23% of HF patients aged ≥ 65 years reside in nursing homes [3]. Nursing homes exist throughout the world, and their residents are easy to identify from their home addresses.

From the very beginning our aim was to include the nursing home residents only, as the high mortality after hip fracture was almost exclusively determined by higher death rates among nursing home residents [3], but the Ethical Committee required inclusion of the sheltered housing residents as well. We therefore kept the two groups of residents separated at randomization to avoid potentially different levels of frailty confusing the results.

No frailty index for elderly hip fracture patients was available. We used the CGA Frailty Index, which was originally validated in older surgical cancer patients, since we had access to almost all of its requested items. We considered it to be the best existing tool, but no validation was made in our population. Originally, the frailty index consists of six

components, but the depression item was not achievable in our study. It was not possible to assess patients' mood at hospital admission due to the acute situation. The CGA Frailty Index matched according to short-term mortality on all the components with the exception of impaired cognition and malnutrition [150].

Subsequently, the assessment by CGA Frailty index showed that a large proportion of the residents in sheltered housing were not frail. Some sheltered housing residents were just as frail as the nursing home residents and may have benefited from the liberal RBC strategy, and few residents from nursing homes were not frail. Therefore it was advantageous to include the sheltered housing residents in this study to uncover the differences in frailty according to type of residence. In the future, we need to find a quick and precise instrument for identifying patients who will benefit from the liberal RBC transfusion strategy.

Pugely et al. suggest a simple risk score calculator to predict 30-day morbidity and mortality after hip fracture surgery. The tool was an internally validated method with the purpose of identifying high-risk patients and informing patients about operative risk. The predictors for major complications and mortality are age greater than 80 years, male gender, ADL-dependency preoperatively, active cancer, and ASA classes 3 and 4 [207]. Furthermore, Laulund et al. found that the biomarkers low Hb, low total leukocyte count, low albumin, and high creatinine at admission are valid predictors of mortality in hip fracture patients [208]. We found the same results for identical biomarkers at admission, except for leukocytes. However, due to the quality of a multivariable logistic regression model, we were only able to enter one variable at a time into the model adjusting for RBC transfusion strategy. This needs to be further investigated in a large cohort study.

Methodological considerations

Strengths and limitations

Observational studies do not take into account the large amount of potential confounders in transfusion and non-transfused patients. It could be argued that RBC transfusions themselves are markers of the severity of illness that cannot be adjusted for by a multivariate analysis. Therefore the experimental element of *random allocation* to an intervention is needed in the frail elderly with a high prevalence of comorbidities, physical impairments, and many other possible confounders. All patients in our RCT study received the same orthogeriatric approach except with regard to the number of RBC units. In addition to the randomized design, the major advantages in our study were that the blood tests were closely followed throughout the whole intervention period of 30 days, and the RBC transfusions were

accomplished within 24 hours; with the exception that transfusions were considered unethical in dying patients.

It has been argued that test of *baseline homogeneity* is philosophically unsound, of no practical value, and potentially misleading [209]. Even though the randomization process had been properly conducted, we tested the baseline homogeneity and found imbalance between groups in the baseline ‘age’ variable. Mean age in the liberal transfusion group was significantly higher than in the restrictive transfusion group. Due to the well-known fact that increasing age is highly associated with mortality, we tested the imbalance and found no association with physical recovery or mortality.

No selection bias intruded since *daily assessments* at the orthopedic ward continued for every hip fracture patient admitted from nursing homes or sheltered housing during the entire study period. Only 2.8% of patients in our study dropped-out compared to a pre-calculated estimate of 10%. Shehata et al. recommend that studies assessing transfusion strategies should report *adherence* rate by physicians and patients, since it will affect the interpretation of outcomes if a high proportion of patients are not transfused according to the strategy [139]. In this study of high-risk cardiac surgery patients, adherence in an intensive care unit was 82% in the restrictive group vs. 69% in the liberal group. In the ward, adherence was 100% in the restrictive group vs. only 14% in the liberal group. Low adherence and no statistically significant difference in Hb levels may have the potential to negatively influence practice and study outcomes. In our TRIFE study the adherence rate was very high (94% in each strategy group).

The allocation of the participants and the Hb measures were *blinded* only for the outcome assessor, the participants, and their relatives. It was not possible to blind the health care professionals. Furthermore, even though it was planned that only one assessor tested each patient during follow-up, in some cases two assessors were involved in testing during follow-up (e.g. one at day 10 and the other at day 30) due to vacation or illness. This might have infected the results although we know that information bias would be equally distributed by the RCT design.

The *sample size calculations* on physical recovery were performed solely on the nursing home residents’ ADL performance 30 days after surgery without taken into account the prefracture measurements. Comparing baseline variables 10 days after surgery was our first idea outlined in the protocol (clinicaltrials.gov). We assumed that recovery from physical disability would quickly respond to the higher Hb level. However, we realized that repeated measurements during 90 days, including the prefracture MBI score, were a better and more precise outcome. It could be argued that our sample size including the non-frail sheltered

housing residents was not large enough to show any improvements, and it is questionable whether the *thresholds interval* in our study was large enough to show any differences. Elderly with healthy hearts and lungs in the restrictive transfusion group may have been treated as the population suited for a RBC transfusion threshold of 4.5 mmol/L (7.2 g/dL) according to the recommendation at that time.

We made *post-hoc analysis* to calculate sample size in mortality and infection outcomes. Based on a previous study from Denmark in which a liberal transfusion strategy in elderly hip fracture patients improved 30-day mortality compared to a restrictive strategy [72], we estimated that a total of 252 patients would be needed to be enrolled to obtain 85% statistical power. Considering the probability of subject resignation, we added 10% to the sample size, yielding a final required number of 277 patients. A post-hoc sample size calculation with 70% power based on risk of all serious infections, combined, showed that 3075 patients were required in each group to prove no type II errors [143]. Unfortunately, it was impossible for us to recruit so many participants, and furthermore it was unethical to continue the recruitment of patients since the survival of the nursing home residents treated according to the liberal transfusion strategy improved. Nevertheless, our analyses showed no tendency at all, suggesting an increase in bacterial infections.

The sample size calculation was based upon the sum-scores of MBI and was therefore our first choice of tool. NMS and CAS measurements were presented in order to make our results comparable to studies using similar tools. MBI was a sensitive *physical assessment* tool and able to measure changes over time, although the items: eating, bowel control, and bladder control were of no relevance for the recovery aspect. The sum-scores of NMS and CAS were not able to measure physical changes in the frail elderly. Instead, transfer and walking ability were more relevant measurements. All measurements were accomplished prospectively; however, the assessor had to measure the prefracture level of physical performance retrospectively and recall bias were possible, when the patients and caregivers were asked to remember 3-4 weeks back in time. It might have infected the results, but we assume that the diversities were distributed equally. The physical ability measurements was set to zero at follow-up if the participant died, and this choice might be questionable when death was not distributed equally in the two groups.

Diagnosis of infection was assessed by the health care professionals at the hospital and the orthogeriatric team who were aware of patient allocation. The infection data were collected by the project manager and obtained from the patients' medical charts. All the assessed infections were treated by antibiotics. Yet, there is no reason to believe that information bias is an important concern for this study. In the general treatment and care, the

health care providers did not give much attention to the patients' allocation, only when the Hb measurements were checked was the allocation important.

Baseline *cognitive status* was assessed with the MMSE; however, it represented a risk of overestimating the diagnosis of cognitive impairment in the acute situation, and therefore we also used the clinical cognitive evaluation undertaken by two independent healthcare professionals.

The DL instrument is intended for measuring *overall QoL* in this specific group of frail elderly and is found reliable and responsive to changes. However, it was only applicable in patients with a MMSE score ≥ 5 who were not in a state of delirium. It meant that 35% of the survivors after 30 days were unable to reply or were unwilling to respond to the questionnaire. Therefore the analyses became underpowered and the OQoL in the very severely demented elderly remains unknown. Those who completed the DL questionnaire were the healthiest and least dependent on personal assistance in the study population. The response rate in hip fracture patients by Rohde et al. was only 52%, even though they excluded patients with confusion or dementia [74]. In another QoL study in nursing home residents, 60% were able to complete the assessing [81], which was similar to our response rate of 65%. Our study did not consider self-reports of pre-fracture OQoL, since we consider such retrospective reports to be unreliable. Nor did we perform pre-fracture proxy QoL-ratings, owing to their very poor correlations with self-reports of cognitively impaired patients [79].

Ethical considerations

Health care professionals want to deliver the most qualitative and appropriate treatment and want concurrently to practice ethically correct. However, in the elderly nursing home residents with limited life expectancy, it can be difficult to determine what is the most appropriate and ethical correct treatment. Decisional conflicts may occur, and physicians will continue to struggle with the dilemma of balancing the primacy of patient welfare, values, and beliefs against the desire for promising, but often minimally beneficial and harmful treatment by limited clinical resources. Despite these challenges, physicians should be able to prescribe systematic medication in their nursing home patients for whom this is consistent with the goals of care [210]. Living in nursing homes is considered to be the 'last stop' in life and sometimes the attitude of society and even in the residents' relatives is that the frail elderly must be allowed to die without too much turbulence when acute disease occurs. However, in this project we found that most of the patients' next of kin accepted signing of

the surrogate consent if the patient was cognitive impaired; only 6% refused. These next of kin obviously wanted their loved one to have the best treatment despite frailty. Furthermore, when surgical repair of a broken hip in the frail elderly patient has been decided upon and carried out, the following treatment should be completed according to comprehensive geriatric assessment and consequent intervention.

Conclusion

A *liberal* RBC transfusion strategy with a hemoglobin threshold of 7 mmol/L (11.3 g/dL) within the first 30 postoperative days after hip fracture surgery in patients admitted from nursing homes and sheltered housing facilities

1. did not improve ADL performance, ambulation, and mobility 10 days after hip fracture surgery, and did not improve the repeated measurements on Modified Barthel Index sum-scores preoperatively and three times during 90 postoperative days,
2. reduced the incidence of deaths measured at 30-day (per-protocol), and reduced 90-day mortality in the nursing home residents (intention-to-treat),
3. did not increase the risk of treatment-required infections within 10 postoperative days, and did not increase the concentrations of leukocytes and C-reactive protein, measured in five repeated blood tests during 30 postoperative days,
4. did not enhance overall QoL 30 days and 365 days after surgery but did improved 1-year recovery of ADL, which was associated with better OQoL

as compared to a *restrictive* strategy of 6 mmol/L (9.7 g/dL).

According to our Hb thresholds, the liberal RBC transfusion strategy seems to improve 90-day survival in the most frail elderly hip fracture patients without increasing the risk of healthcare-associated infections or impairing physical recovery compared to a restrictive strategy. Even though we did not find better overall QoL in patients treated according to the liberal strategy, the liberal strategy seemed to improve recovery of physical performance within 1 year after hip fracture surgery and this was associated with a better overall QoL.

We recommend that the guidelines for red blood cell transfusions in hip fracture patients should be reconsidered in favor of the frailest elderly.

Future aspects

- A liberal RBC transfusion strategy combined with a comprehensive geriatric approach in frail elderly (e.g. nursing home residents) seems to be life-saving without reducing physical recovery, overall QoL, and without increasing risk of infections. Further important benefits need to be investigated.
- It would be relevant to compare Hb targets with a larger discrepancy than in our study in order to examine the effect of the liberal RBC transfusion threshold at 7 mmol/L (11.3 g/dL) compared to the new restrictive transfusion threshold as low as 4.3 mmol/L (7.0 g/dL) in patients with a stable circulatory system and without heart disease, < 5.0 mmol/L (8 g/dL) in patients with chronic heart disease, and < 5.6 mmol/L (9 g/dL) in patients with acute ischemic syndrome or life-threatening bleeding.
- Frail elderly hip fracture patients with a high risk of mortality-associated complications should not be grouped with healthy elderly in studies targeted interventions to improve quality of geriatric treatment and care and determine sufficient rehabilitation.
- Development and validation of a new 'frailty index' designed for the elderly hip fracture patients would seem desirable with the purpose of distinguishing the frail from the non-frail patients. This may be of use in orthopedic departments to easily identify the relevant patient who needs a transfusion of red blood cells.

Summary in English

Hip fracture in the elderly is associated with poor recovery from physical disability and mortality. Perioperative blood loss is common, and anemia might be fatal in the frail elderly. Red blood cell transfusions might increase the risk of infection. In an observational study, a liberal transfusion strategy with hemoglobin (Hb) target of 7 mmol/L (11.3 g/dL) seemed to improve survival in nursing home residents with hip fracture compared to the recommended restrictive strategy with a Hb target of 6 mmol/L (9.7 g/dL) according to the Danish Health and Medicine Authority. Our aim was to compare these two strategies in the frail elderly in a randomized controlled trial on the outcomes: recovery from physical disabilities, mortality, infection, infection biomarkers, and overall Quality of Life (OQoL).

We included 284 elderly admitted to hospital for surgical hip fracture repair from nursing homes or sheltered housing facilities. The anemic patients were assigned postoperatively to the liberal or the restrictive transfusion strategy. Randomization divided each transfusion group into two equal blocks with regard to type of the residence. Hb was measured daily during the first 3 postoperative days, at least once during the following 4 to 6 days, then at least once a week during the subsequent 3 weeks. The transfusions were administered according to group assignments, but no later than 24 hours after the Hb determination, one unit at a time, and no more than two units per day. The intervention lasted for 30 days after surgery. Outcome measurements were performed on days 10, 30, 90, and 365. Blinded assessors evaluated physical performance and OQoL.

The liberal transfusion strategy did not improve recovery from physical disabilities, mortality, infection rate, or OQoL compared to the restrictive strategy. However, in nursing home residents, 90-day mortality rate (20%) following the liberal strategy was statistically significantly lower than that (36%) after the restrictive strategy. Per protocol, the 30-day mortality rate was statistically significantly lower following the liberal strategy in all patients (7% versus 16%). No statistically significant difference was found in repeated leukocyte counts and C-reactive protein measurements, or in rate of all infections after 10 days (66% versus 72%). Physical recovery from 30 days until 1 year after hip fracture surgery was improved by the liberal strategy. A liberal strategy did not improve 30-day OQoL. Physical performance was improved from 30 days to 1 year after fracture in patients treated according to the liberal strategy and was associated with better progress of OQoL in the same period.

We conclude that according to our used Hb thresholds, the liberal Hb target of 7 mmol/L (11.3 g/dL) improves survival in the frailest elderly (the nursing home residents) without impairing recovery from physical disabilities and OQoL, or increasing risk of infections compared to the restrictive Hb target of 6 mmol/L (9.7 g/dL). The liberal strategy seems to improve recovery of physical performance within 1 year after hip fracture surgery which was associated with better overall QoL.

Summary in Danish/ Dansk resumé

Hoftefraktur hos ældre er associeret med forringet evne til at genvinde fysisk funktionsevne og dødelighed. Blodtab under og efter operation forekommer hyppigt og anæmi kan blive fatalt hos den skrøbelige ældre patient. I et observationelt studie har vi tidligere fundet, at en liberal transfusionsstrategi med en hæmoglobin (Hb) grænse på 7 mmol/L ser ud til at øge overlevelsen hos ældre fra plejebolig med hoftefraktur sammenlignet med Sundhedsstyrelsens restriktive strategi med en Hb grænse på 6 mmol/L. Vores mål var at sammenligne de to transfusionsstrategier hos de skrøbelige ældre i et klinisk randomiseret kontrolleret forsøg med effektmålene: restitution efter fysisk funktionsnedsættelse, dødelighed, infektion, biomarkører for infektion, og overordnet livskvalitet.

Vi inkluderede 284 ældre med hoftebrud indlagt fra pleje- og ældrebolig til operativ behandling på hospitalet. De anæmiske patienter blev ved lodtrækning efter operationen fordelt til enten den liberale eller den restriktive transfusionsgruppe. Randomiseringen stratificerede hver transfusionsgruppe i to ens blokke i forhold til boligtype og køn. Gennem de første tre postoperative dage blev Hb målt dagligt, herefter mindst én gang de følgende fire til seks dage og mindst én gang om ugen de følgende tre uger. Blodtransfusion blev administreret ifølge gruppeltildelingen senest 24 timer efter den aktuelle Hb måling, én portion ad gangen og ikke mere end to portioner om dagen. Interventionen varede frem til 30 dage efter operation. Måling af effektparametrene blev udført på dag 10, 30, 90 og 365. To blindede observatører evaluerede den fysiske funktionsevne og den overordnede livskvalitet.

Den liberale transfusionsstrategi forbedrede ikke den fysiske funktionsevne, overlevelsen, infektionsraten eller den overordnede livskvalitet i forhold til den restriktive strategi. Men hos ældre fra plejebolig var 90-dags dødeligheden (20%) statistisk signifikant lavere ved en liberal transfusionsgrænse end ved en restriktiv grænse (36%). Per protokol var 30-dags dødeligheden statistisk signifikant lavere ved en liberal transfusionsstrategi end ved en restriktiv strategi målt hos alle patienter (7% versus 16%). Vi fandt ingen statistisk signifikant forskel ved de gentagne målinger af leukocytter og C-reaktiv protein i blodet eller ved infektionsraten efter 10 dage (66% versus 72%). En liberal strategi forbedrede ikke livskvaliteten efter 30 dage. Restitutionen efter fysisk funktionsnedsættelse blev forbedret fra dag 30 frem til et år efter frakturen ved en liberal strategi sammenlignet med en restriktiv strategi og var associeret med en fremgang i livskvalitet indenfor den samme periode.

Vi konkluderer i forhold til vores anvendte transfusionsgrænser, at en Hb grænse på 7 mmol/L øger overlevelsen hos de mest skrøbelige patienter (patienter fra plejebolig) uden at forringe den fysiske funktionsevne, den overordnede livskvalitet, og uden at øge risikoen for infektion sammenlignet med en restriktiv grænse på 6 mmol/L. En liberal strategi ser ud til at forbedre restitution efter fysisk funktionsnedsættelse indenfor et år efter hoftefraktur, hvilket er associeret med en fremgang i livskvalitet.

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Appendix 1

	PubMed	Embase	Cinahl	The Cochrane Library
Population	Combined with 'OR': 'Aged' [MeSH] 'Elderly' (free text) 'Housing for the Elderly' [MeSH] 'Nursing Homes' [MeSH] 'Comorbidity' [MeSH] 'Cognition Disorders' [MeSH] 'Wounds and Injuries' [MeSH] 'Hip fractures'[MeSH]	Combined with 'OR': 'Aged' [Emtree] 'Elderly' (free text) 'nursing home' [Emtree] 'home for aged' [Emtree] 'cognition defect' [Emtree] 'morbidity' [Emtree] 'hip injury' [Emtree]	Combined with 'OR': 'Elderly' (free text) 'Aged' (Cinahl Headings [CH]) 'Nursing Homes' [CH] 'Housing for the Elderly' [CH] 'Cognition Disorders' [CH] 'Morbidity' [CH] Hip fractures' [CH] 'Wound and Injuries' [CH]	Combined with 'OR': 'Elderly (free text) 'Aged' [MeSH] 'Cognition disorder' [Mesh] 'Morbidity' [MeSH] 'Hip fractures' [MeSH]
Intervention	Combined with 'OR': 'Blood transfusions' [MeSH] 'Geriatric Assessment' [MeSH] 'Geriatrics' [MeSH]	Combined with 'OR': 'blood transfusion' [Emtree] 'geriatric assessment' [Emtree] 'geriatrics' [Emtree]	Combined with 'OR': 'Blood Transfusion' [CH] 'Geriatric Assessment' [CH] 'Geriatrics' [CH]	'Blood Transfusion' [MeSH] 'Geriatric Assessment' [Mesh] 'Geriatrics' [MeSH]
Comparison	Combined with 'OR': 'Anemia' [MeSH] 'Anaemia' (free text) 'Policy' [MeSH] 'Health planning guidelines' [MeSH]	Combined with 'OR': 'anemia' [Emtree] 'anaemia' (free text) 'policy' [Emtree] 'practice guideline' [Emtree]	Combined with 'OR': 'Anemia' [CH] 'Anaemia' (free text) 'Hospital Policies' [CH] 'Practice Guidelines' [CH]	'Anemia' [MeSH] 'Policy' [MeSH] 'Health Planning Guidelines' [MeSH]
Outcomes				
1. Physical recovery	Combined with 'OR': 'Early Ambulation' [MeSH] 'Mobility Limitation' [MeSH] 'Activities of Daily Living' [MeSH] 'Rehabilitation' [MeSH] 'Quality of Life'[MeSH]	Combined with 'OR': 'daily life activity' [Emtree] 'mobilization' [Emtree] 'walking difficulty' [Emtree] 'rehabilitation'[Emtree] 'quality of life' [Emtree]	Combined with 'OR': 'Activities of Daily Living' [CH] 'Early Ambulation' [CH] 'Physical mobility' [CH] 'Rehabilitation' [CH] 'Quality of Life' [CH]	Combined with OR: 'Activities of Daily Living' [MeSH] 'Early Ambulation' [MeSH] 'Mobility Limitation' [Mesh] 'Rehabilitation' [MeSH] 'Quality of Life'[MeSH]
2. Mortality	'Mortality' [MeSH]	'mortality' [Emtree]	'Mortality' [CH]	'Mortality' [MeSH]
3. Infection risk	'Infection Risk' [MeSH] 'Patient Readmission' [MeSH] 'Immunomodulation' [MeSH] 'Immunosuppression' [MeSH]	'infection' [Emtree] 'risk' [Emtree] 'hospital readmission' [Emtree] 'immunomodulation' [Emtree] 'immunosuppressive treatment' [Emtree]	'Infection' [CH] 'Risk for injury' [CH] 'Immunologic Factors' [CH] 'Immunosuppression' [CH]	'Infection' [MeSH] 'Risk' [MeSH] 'Immunomodulation' [MeSH] 'Immunosuppression' [MeSH]

	Pubmed	Embase	Cinahl	The Cochrane Library
Antal hits	870	452	25	59
Antal udvalgte artikler	121	63 (18 duplicates)	6 (1 duplicate)	9 (2 duplicates)

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