condition (e.g., cancer). For example, 91.1% of patients who received MT in the setting of malignant disease (nonsurgical) died within 5 years. In contrast, in cases of MT during obstetrical hemorrhage, which generally occurs in young and healthy individuals, mortality was only 1.7% through 5 years. In addition, they also found that standardized mortality ratios (indexed to the general population) remained quite high even out to 5 to 10 years after the MT. This, however, does not imply causation between the receipt of many units of RBCs and long-term mortality because patients with more severe injury/illness who bleed significantly will certainly be at risk for complications, fore example, acute/renal failure, that will adversely impact their long-term prognosis. The authors were unable to assess whether the transfusions per se, independent of disease severity/comorbidities, were associated with adverse outcome.

Bleeding and the need for transfusion are still major issues affecting ICU patients. The study by Halmin et al (10) is a step in the right direction because it will help focus our research and quality improvement efforts on the patients in whom MT is occurring most frequently.

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Massive Transfusion: An Issue for Us All*

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In this issue of *Critical Care Medicine*, Halmin et al (1) provide a sweeping descriptive overview of the transfusion practices within two countries over the past two decades. Although this type of descriptive study has some limitations, many related to the inability for granular data analysis, it provides some important insight into global transfusion practices on a national level. Using a national database, they describe the short- and long-term outcomes on over 92,000 patients who were transfused more than two million blood products over nearly two decades. Interestingly, they report a long-term association with higher standardized mortality rates in most age groups and a relatively stable prevalence of massive transfusion (MT) although slightly different in the two countries. They also note that the majority of MT episodes are not trauma related, at least in these two countries. These last conclusion is important because the vast majority of the robust recent literature on prevalence and outcomes after MT are within the trauma literature and have a much more narrow focus. Indeed, it remains unclear whether patients who require MT for other indications truly benefit from empiric high fixed ratio resuscitation, which was designed to combat the increasingly well-characterized acute traumatic coagulopathy associated with severe, multisystem injury (2).

***See also p. 468.**

Key Words: massive transfusion; resuscitation; trauma

The author has disclosed that he does not have any potential conflicts of interest.

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The most important aspect of this article relates to resource deployment and utilization. What is not discussed often enough in the trauma literature is the massive resource utilization required to properly follow a protocol designed to provide a patient with large quantities of blood components in specific ratios in an emergent situation. Indeed, smaller institutions with smaller blood banks are often unable to provide the necessary resources to thaw, prepare, and transfuse patients in acceptable ratios on the rare occasion they face these challenging patients (3). Despite this fact, increasing emphasis is placed on acceptable transfusion practices in the setting of MT in terms of trauma center verification in the United States. The fact that this article suggests that the number of patients requiring MT after trauma in both acute (< 24 hr) and subacute (24–48 hr) situations is dwarfed by the number of patients requiring the same for nontraumatic indications calls for a more global thought process when an institution, region, and nation think about how to set up and deploy protocols designed to tax what is already a relatively scarce resource.

One of the most important aspects of resource utilization is early and accurate diagnosis of the need for a therapy. In the decision to activate a MT protocol, the astute clinician must weigh many factors including both an individual patient's status and available resources. Indeed, for the trauma patient, there are several scoring systems and predictive models that have been designed to assist clinicians in this complex, time-sensitive decision. Some are simple, using a few nominal variables that are available to the clinician at the bedside (4) and others are more complex, using scoring systems that, while designed to be calculated manually, cannot be readily used by a clinician in real time (5) Finally, one clinical decision support tool is based on a complex statistical model packaged into a Smart Phone application that provides a clinician a robust prediction of the need for MT based on a few simple variables available on presentation (6). All of these models, however, are designed to assess a patient's need for MT after trauma, and none of them have been extensively validated across institutions. Perhaps, a more global clinical decision support tool to assist clinicians at the bedside caring for both injured and noninjured patients at risk for MT is warranted.

Finally, the implications of this article are that a more organized and global approach to MT is required, and data analysis across an entire system of healthcare delivery is necessary to provide insight in the efficient utilization of this resource. For instance, it is not truly known what proportion of MT is related to trauma in the United States. Indeed, the definition of MT is still debated. It is likely that different subsets of patients requiring aggressive component therapy over a short time frame have specific needs and efficient resuscitation of these subgroups requiring tailoring to these factors. Furthering our knowledge in this field will allow for the most efficient resuscitation not only on the individual patient level but also on a systems level.

All in all, Halmin et al (1) provide a useful global view of transfusion practices on a national level. Furthering our global understanding of transfusion practices across systems should allow for improved and efficient patient care.

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Patients With Massive Transfusion: Who Are You?*

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Transfusion of RBCs is one of the most common medical procedures, occurring in 12% of U.S. hospital stays with a procedure (1). It is also consumes valuable healthcare resources, with one analysis reporting a range of $522 to $1,183 for the total cost per RBC unit administration (2). There is no doubt that the administration of stored allogeneic RBCs can be lifesaving in patients with profoundly low hemoglobin levels, for example, 2 g/dL. However, many questions related to RBC transfusion remain unanswered.

A major unresolved controversy surrounding RBC transfusion is whether the administration of blood to patients with moderate levels of anemia (8–10 g/dL) is beneficial or even safe. The Transfusion Requirements in Critical Care (TRICC) trial, which failed to show improved outcome in critically ill patients after liberal RBC transfusion, highlighted the point that "more is not always better" when it comes to allogeneic blood administration (3). Another controversy involves the clinical relevance of the "storage lesion" that develops in banked RBCs (4). Recent randomized studies show that the administration of "young" RBCs is not better than "middle-aged" RBCs (5, 6); however, these trials did not address the safety and efficacy of "old" blood nearing the 42-day shelf life. RBC transfusion to increase arterial oxygen content and presumably tissue oxygenation has also been a component of goal-directed therapy in patients with sepsis. Although the initial trial by Rivers et al (7) showed a benefit to this care, subsequent large multicenter studies have failed to confirm a benefit of goal-directed therapy including RBC transfusion (8, 9).

Another important aspect of transfusion medicine is massive transfusion (MT), which is the focus of the study by Halmin et al (10) in this issue of *Critical Care Medicine*. MT, often defined as the administration of at least 10 units of RBCs in a 24-hour period (11), is clearly associated with adverse outcome. It has been difficult, however, to tease out the extent to which the transfusions per se, independent of the underlying injury/illness, contribute to higher mortality in these patients. Trauma patients were the initial focus of studies and quality improvement initiatives (often called massive transfusion protocol [MTP]). MTPs focus on several processes of care including availability of adequate volumes of blood products and in many cases a set ratio of RBC to plasma to platelets (12). It was widely believed (mostly anecdotal) that most MT was occurring in trauma and patients with obstetrical emergencies. Until now, there has been scant descriptive data addressing "Who are the patients with MT?"

Fortunately, the study by Halmin et al (10) makes an admirable start at addressing this gap in the literature. They leveraged large administrative databases in Sweden and Denmark to assess what types of patients received large numbers of RBC units, and the corresponding short-term (30 d) and long-term (> 10 yr) mortality in these patients. Patients who received an RBC transfusion in Sweden from 1987 to 2010 were included as were those in Denmark from 1996 to 2010. The database (SCANDAT2) included 1,731,906 cases where at least 1 RBC unit was transfused (Supplementary Table 1 in [10]). Of these cases, 92,057 (5.3%) received at least 10 RBC units within a 7-day period and were considered MT by the authors. In an attempt to allow some generalizability to previous studies of MT, they subdivided these cases into "acute" MT (n = 53,836), defined as receiving at least 10 RBC units with 2 calendar days, versus "nonacute" MT (n = 38,221), defined as receiving at least 10 RBCs units over a longer period of time (≤ 7 d). The dataset did not contain the time (hr) of administration, which precluded use of the traditional definition of MT (10 units within 24 hr). Fortunately, their main results on the indication for MT are markedly consistent across acute and nonacute MT cases. Furthermore, a sensitivity analysis revealed that approximately half of the acute MT cases received the 10 RBC units within 1 calendar day supporting the notion that these cases involved acute bleeding.

The primary and most important finding is that major surgery was the most common indication for MT (61.2% of cases), with trauma playing a lesser role (15.4%), and obstetrical emergencies barely registering at only 1.8% of all MT cases. This important result was consistent across both acute and nonacute MT cases. On the basis of these data, investigators and quality experts should broaden the net for MT and include patients undergoing major surgery in particular. This is not to say that there is no need for MTPs in obstetrics; rather, this study highlights the fact that efforts should certainly include other types of at-risk patients.

The study has other interesting findings. The prevalence of MT occurred at a similar rate over the 13-year period (1987–2010) (Fig. 1 in [10]), which may be disappointing but very useful news to those focused on efforts to reduce the likelihood of these events. The study's mortality analyses has two main results. Death at 5 years was highly variable by indication and related to the patient's underlying illness/

*See also p. 468.

Key Words: blood; critically ill; massive transfusion

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Bleeding and the need for transfusion are still major issues affecting ICU patients. The study by Halmin et al (10) is a step in the right direction because it will help focus our research and quality improvement efforts on the patients in whom MT is occurring most frequently.

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Massive Transfusion: An Issue for Us All*

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In this issue of *Critical Care Medicine*, Halmin et al (1) provide a sweeping descriptive overview of the transfusion practices within two countries over the past two decades. Although this type of descriptive study has some limitations, many related to the inability for granular data analysis, it provides some important insight into global transfusion practices on a national level. Using a national database, they describe the short- and long-term outcomes on over 92,000 patients who were transfused more than two million blood products over nearly two decades. Interestingly, they report a long-term association with higher standardized mortality rates in most age groups and a relatively stable prevalence of massive transfusion (MT) although slightly different in the two countries. They also note that the majority of MT episodes are not trauma related, at least in these two countries. These last conclusion is important because the vast majority of the robust recent literature on prevalence and outcomes after MT are within the trauma literature and have a much more narrow focus. Indeed, it remains unclear whether patients who require MT for other indications truly benefit from empiric high fixed ratio resuscitation, which was designed to combat the increasingly well-characterized acute traumatic coagulopathy associated with severe, multisystem injury (2).

***See also p. 468.**

Key Words: massive transfusion; resuscitation; trauma

The author has disclosed that he does not have any potential conflicts of interest.

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Epidemiology of Massive Transfusion: A Binational Study From Sweden and Denmark*

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Objective: There is an increasing focus on massive transfusion, but there is a paucity of comprehensive descriptions of the massively transfused patients and their outcomes. The objective of this study is to describe the incidence rate of massive transfusion, patient characteristics, and the mortality of massively transfused patients.

Design: Descriptive cohort study.

Setting: Nationwide study with data from Sweden and Denmark.

Patients: The study was based on the Scandinavian Donations and Transfusions database, including all patients receiving 10 or more red cell concentrate transfusions in Sweden from 1987 and in Denmark from 1996. A total of 92,057 patients were included. Patients were followed until the end of 2012.

Measurements and Main Results: Descriptive statistics were used to characterize the patients and indications. Post transfusion mortality was expressed as crude 30-day mortality and as long-term mortality using the Kaplan-Meier method and using standardized mortality ratios. The incidence of massive transfusion was higher in Denmark (4.5 per 10,000) than in Sweden (2.5 per 10,000). The most common indication for massive transfusion was major surgery (61.2%) followed by trauma (15.4%). Massive transfusion due to obstetrical bleeding constituted only 1.8%. The overall 5-year mortality was very high (54.6%), however with large differences between indication groups, ranging from 91.1% among those transfused for a malignant disease without surgery to 1.7% among patients transfused for obstetrical bleeding. The early standardized mortality ratios were high and decreased thereafter, but remained elevated throughout the time period.

Conclusions: This large-scale study based on nationwide data from Sweden and Denmark describes the complete range of massive transfusion. We report a nonnegligible incidence and both a high absolute mortality and high standardized mortality ratio. The general pattern was similar for Sweden and Denmark, and we believe that similar patterns may be found in other high-resource countries. The study provides a relevant background for clinicians and researchers for designing future studies in this field. (*Crit Care Med* 2016; 44:468–477)

Key Words: epidemiology; incidence; massive hemorrhage; massive transfusion; survival; trauma

***See also p. 631 and p. 632.**

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Massive hemorrhage is the second most common cause of trauma-related death (1) and contributes considerably to the mortality associated with any kind of surgery (2). The treatment, in addition to bleeding control, is massive blood transfusion. This is commonly defined as receipt of 10 or more red cell products during a 24-hour period (3), but a variety of definitions have been applied in studies, and the relevance of the different definitions has been questioned (4–6). In particular, the risk of introducing a selection bias, by not including patients who exsanguinate early after admission to hospital and who would, therefore, not survive long enough to receive the arbitrary number of sufficient transfusion to fulfill the definition, has been highlighted (7).

In recent years, protocols for massive transfusion have gained increasing attention, especially with regard to the use of plasma and platelets for trauma-related massive hemorrhage (7). At the same time, possible risks associated with massive transfusion have been discussed and associations with both increased morbidity and mortality have been observed (8).

According to the literature, the main indications for massive transfusions are trauma, obstetrical or gastrointestinal bleeding, and major surgery (9, 10); however, there is a paucity of reliable data regarding how frequent massive transfusion is in different patient groups. In fact, beyond trauma, cardiac surgery, and to lesser extent obstetrical patients, there are virtually no data available on massively transfused patients. Indeed, the overall population of massively transfused patients thus remains poorly characterized. As the paucity of a comprehensive description of massively transfused patients limits our understanding of this patient group and the ability to design and conduct research on these patients, we decided to perform an epidemiologic study focused on describing the wider panorama of massively transfused patients with the specific aim to identify what patient groups experience massive transfusion and what the expected outcome is for these patients.

METHOD

Data Sources

The analyses were based on the Scandinavian Donations and Transfusions (SCANDAT2) database, which has been described in greater detail previously (11). In brief, the electronic registration of data on blood donation, blood components, and transfused patients was initiated in 1968 in Sweden and 1983 in Denmark. Although electronic registration was only used by a limited number of blood centers, the proportion has increased gradually over time and has been nearly nationwide since 1996 in Sweden and 1998 in Denmark.

All persons in the SCANDAT2 database are identified by unique national registration numbers, enabling linkage with various nationwide health outcomes registers, including the respective country's patient registers which record data on all hospitalizations including date of admission and discharge, main diagnosis, and codes for any surgical procedures. Linkage with population registers provided dates of birth and, where applicable, death and emigration.

The creation of the SCANDAT2 database, as well as the conduct of this study, was approved by appropriate regional ethic committees and data protection agencies in the two countries.

Study Population

We included all massively transfused patients between 1987 and 2010 in Sweden and between 1996 and 2010 in Denmark. In Sweden, earlier data were not considered because the Swedish inpatient register was not nationally complete until 1987, and in Denmark, we deemed that the coverage of the SCANDAT2 database before 1996 was too limited to allow a meaningful complete characterization of the massive transfusion incidence. We defined massive transfusion as receiving 10 RBC concentrates or more. Because transfusions are only recorded by calendar day in SCANDAT2, it is impossible to calculate the number of transfusions administered over exactly 24 hours. We, therefore, defined acutely massively transfused patients as those who had received 10 or more RBCs over two consecutive calendar days as a compromise. We performed a sensitivity analysis using receipt of 10 RBC or more during 1 calendar day, as an alternative definition. In addition, we also employed a variant definition of massive transfusion where patients received 10 or more RBCs within a period of 7 calendar days, henceforth referred to as "nonacute massive transfusion." Because patients occasionally received massive transfusions more than once, we allowed patients to contribute more than one massive transfusion episode. Two transfusion episodes were considered independent of each other, if they were separated by intervals of at least 7 days of no transfusion activity.

To establish the underlying indication for the massive transfusion, which was not explicitly recorded in the SCANDAT2 database, we expanded a previously used algorithm (12). This algorithm is based on a combination of the main discharge diagnosis (coded using the *International Classification of Disease* [ICD], revisions 9 and 10) for each hospital contact and any surgical codes used and yields nine indication groups: 1) trauma; 2) nontrauma, obstetric care; 3) nontrauma, nonobstetric, cardiac/vascular surgery; 4) nontrauma, nonobstetric, noncardiac/vascular, cancer surgery; 5) nontrauma, nonobstetric, noncardiac/vascular, noncancer surgery, other surgery; 6) other care for hematologic malignancy; 7) care for other malignant disease; 8) other hospital care; or 9) no data available. According to this algorithm, a patient with a trauma code (i.e., a code indicating noniatrogenic, external cause of injury) was assumed to have been transfused for trauma, irrespective of other diagnosis codes, and a patient without a code for trauma, but with an obstetric code, was assumed to have been transfused for an obstetrical procedure or complication. The majority of patients had more than one ICD code but were only considered once according to the algorithm. We also reviewed diagnosis codes in the group "other hospital care." Finally, we also extracted data on all transfused patients to enable us to calculate the proportion of all transfused patients during the study period who were massively transfused.

Statistical Analysis

Because the coverage of the SCANDAT2 database was not nationwide from the beginning of the study period, incidence rates of massive transfusion was estimated using a modified background population which included only counties (administrative region) that were fully covered by the database at that time. Incidence rates were stratified by calendar period, country, age, and indication.

The number of transfusions per episode, both overall and by type of blood component, was summarized as medians and interquartile range (IQR). We also categorized the number of blood components given per episode as low (10–19 U), medium (20–49 U), or high (≥ 50 U). We considered five age categories: younger than 18 years, 18–39 years, 40–64 years, 65–79 years, or 80+ years. Calendar year of transfusion was considered both as a continuous variable and categorized (1987–1995, 1996–2000, 2001–2005, or 2006–2010).

In the survival analyses, we followed patients from the last day of the first massive transfusion episode until date of migration, death, or end of follow-up (December 31, 2012), whichever occurred first. Mortality was expressed both as crude 30-day mortality, counted from the last day of blood transfusion in each episode, and as long-term mortality using the Kaplan-Meier method. CIs for the 5-year survival were constructed using a normal approximation to the binomial distribution (13). In the long-term analysis, follow-up was extended for up to 15 years. We also calculated standardized mortality ratios (SMR) for the massively transfused population as the ratio of observed to expected number of deaths where the expected number of deaths were calculated by multiplying the 1-year calendar period-, age-, and sex-specific follow-up time in the cohort with corresponding stratum-specific mortality rates in the general population. CIs for the SMRs were constructed assuming a Poisson distribution (14). The statistical analyses were conducted using SAS statistical software, version 9.3 (SAS Institute, Cary, NC), and Stata statistical software, version 12.1 (StataCorp, College Station, TX).

RESULTS

Altogether, we identified 92,057 individuals who experienced a total of 97,972 episodes of massive transfusion during which 2,305,698 blood components were administered. The episodes of massive transfusion constituted 5.3% of all transfusion episodes during the study period, ranging from 1.7% of those transfused for "other malignant disease" to 5.1% for those transfused for trauma, and 14.4% for those transfused for cardiac/vascular surgery (**Supplementary Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/B528). Of all massive episodes, 56,711 (57.9%) were acute and 41,261 (42.1%) were nonacute. The massively transfused patients received 13.3% of all transfusions in the two countries during the study period.

The general characteristics of massively transfused patients are described in **Table 1**. The median age of the patients was 68 years (IQR, 56–77). Almost two thirds of patients were male (63.8%). The 4,839 patients who experienced more than one massive transfusion episode differed from those being transfused only once by being younger at the time of the first episode, with a median age of 65 (IQR, 53–75), and more often male (69.4%) and by less frequently experiencing acute massive transfusion, 48.6% of all the repeated massive transfusions.

TABLE 1. Characteristics of Study Population

	Acute	Nonacute
No. of subjects (% of total)	53,836 (58.5)	38,221 (41.5)
Females, *n* (%)	18,556 (34.5)	14,754 (38.6)
Sweden, *n* (%)	35,356 (65.7)	22,232 (58.2)
Calendar year of transfusion, *n* (%)		
1987–1995	11,000 (20.4)	6,181 (16.2)
1996–2000	14,593 (27.1)	11,019 (28.8)
2001–2005	14,570 (27.1)	11,179 (29.3)
2006–2010	13,672 (25.4)	9,831 (25.7)
Age at transfusion, yr, *n* (%)		
< 18	775 (1.4)	584 (1.5)
18–39	5,569 (10.3)	2,602 (6.8)
40–64	17,166 (31.9)	11,482 (30.0)
65–79	22,820 (42.4)	15,442 (40.4)
80+	7,506 (13.9)	8,111 (21.2)
Median age (IQR)	67 (54–76)	70 (57–78)
Origin, *n* (%)		
Other country (outside Sweden/Denmark)	4,632 (8.6)	2,711 (7.1)
Indications, *n* (%)		
Trauma	8,386 (15.6)	5,788 (15.1)
Obstetric care	1,408 (2.6)	278 (0.7)
Cardiac/vascular surgery	18,725 (34.8)	6,334 (16.6)
Cancer surgery	5,828 (10.8)	3,405 (8.9)
Other surgery	12,270 (22.8)	9,835 (25.7)
Hematologic malignancy	676 (1.3)	3,096 (8.1)
Other malignant disease	607 (1.1)	1,269 (3.3)
Other hospital care	5,131 (9.5)	7,585 (19.9)
No data available	805 (1.5)	631 (1.7)
Transfusions per episode, median (IQR)	22 (16–33)	16 (12–22)
Red cells concentrates	13 (11–18)	11 (10–14)
Plasma units	7 (4–13)	3 (0–7)
Platelet concentrates	0 (0–2)	0 (0–1)

IQR = interquartile range.

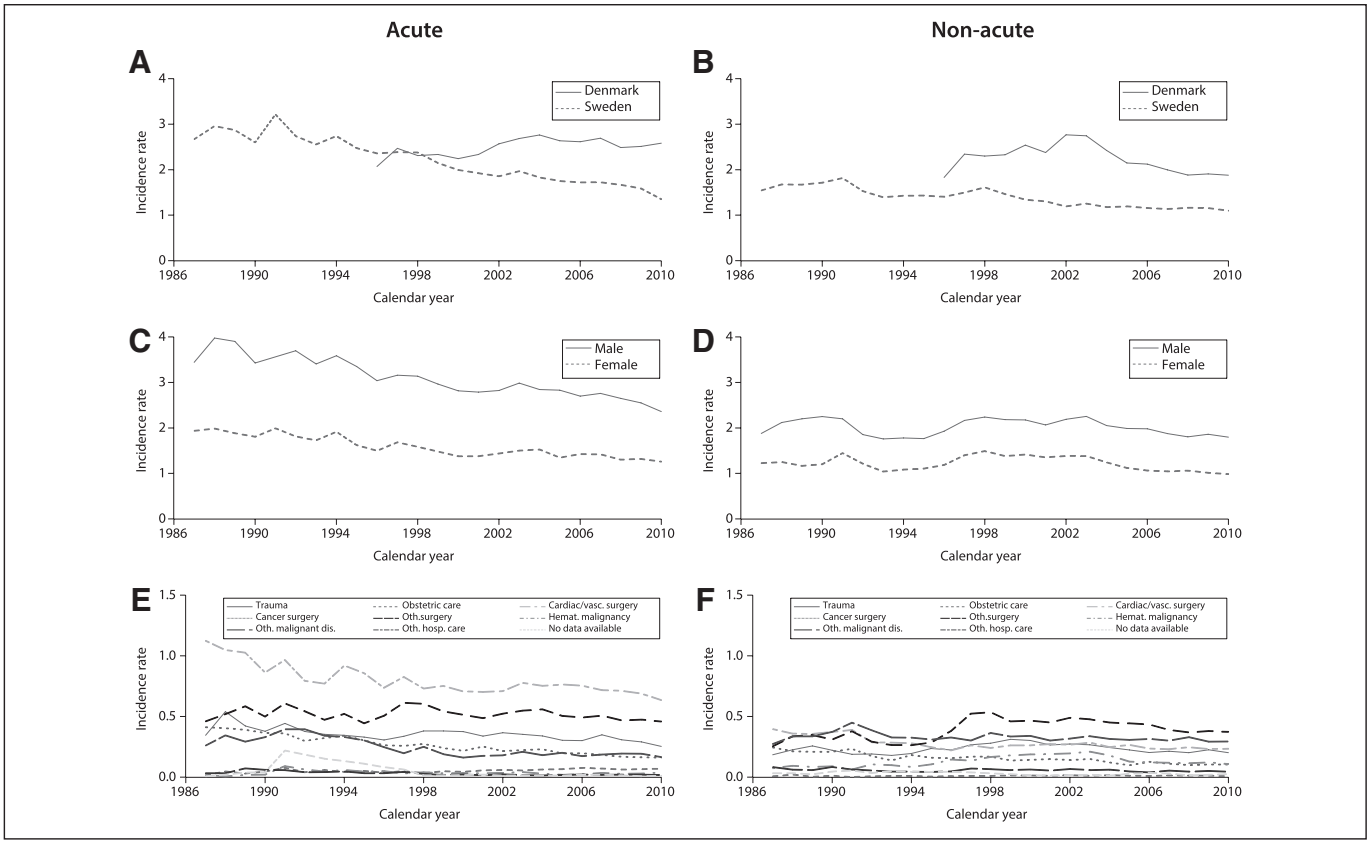

Figure 1. Incidence rates of massive transfusion per 10,000 person years over time (1987–2010). **A**, Acute massive transfusion (≥ 10 RBC within 2 calendar days) for Sweden and Denmark. **B**, Nonacute massive transfusion (≥ 10 RBC within 7 calendar days) for Sweden and Denmark. **C**, Acute massive transfusion (≥ 10 RBC within 2 calendar days) for men and women. **D**, Nonacute massive transfusion (≥ 10 RBC within 7 calendar days) for men and women. **E**, Acute massive transfusion (≥ 10 RBC within 2 calendar days), stratified by indications (trauma, obstetric care, cardiac/vascular surgery, malignant surgery, other surgery, hematological malignancy, other malignant disease, other hospital care, no data available). **F**, Nonacute massive transfusion (≥ 10 RBC within 7 calendar days), stratified by indications (trauma, obstetric care, cardiac/vascular surgery, malignant surgery, other surgery, hematological malignancy, other malignant disease, other hospital care, no data available).

Overall, the distribution of indications was quite similar between Sweden and Denmark, but with some notable differences. A slightly higher proportion of patients were transfused for trauma in Sweden than in Denmark (16.2% vs 14.0%) and the proportion of "other surgery" was larger in Denmark (30.0% vs 20.4%).

Disregarding "obstetric care," where only women are represented, there were no large differences between men and women in the distribution of the different indications (data not shown). The age distribution differed between the indication groups with "trauma" being the most common indication in younger age groups and "cardiac/vascular surgery" being the most common indication in elderly. When the acute group was restricted to patients massively transfused on 1 calendar day, 25,039 subjects (46.5%) remained in the analysis. Slightly higher proportions of trauma (16.4% vs 15.6%) and obstetric care (3.2% vs 2.6%) as indications were noted in those massively transfused on 1 calendar day and the proportion of males was marginally higher, 67.8% versus 65.5%. Manual review of diagnoses in the group of "other hospital care" showed that gastrointestinal bleeding was the single most common indication among these, making up 36.1%. The group with no available data constituted only 1.6% of the total study population and mostly comprised patients transfused before 1996.

Figures 1 and **2** present the incidence rate of massive transfusion over calendar time and age, respectively. The annual incidence of massive transfusion decreased from 4.2 to 2.4 per 10,000 person years between 1987 and 2010 in Sweden, whereas in Denmark, it increased slightly from 3.9 to 4.5 per 10,000 person years between 1996 and 2010. The ratio of acute to nonacute massive transfusion events remained stable over time in Sweden, whereas in Denmark, it increased with time. The distribution of the incidence of massive transfusion for different indications remained relatively stable over time in both countries. In 2010, the highest incidence was seen for cardiac/vascular surgery with 1.0 per 10,000 person years in Denmark and 0.5 per 10,000 person years in Sweden.

Age-specific incidence patterns differed between men and women. Specifically after being similar until age 36 where the annual incidence rates were 1.4 and 1.3/10,000 persons for men and women, respectively; it increased more in men than in women to peak at 25.0/10,000 among men aged 80 and 9.2/10,000 among women of the same age. The incidence rate increased with age exhibiting a similar pattern for almost all

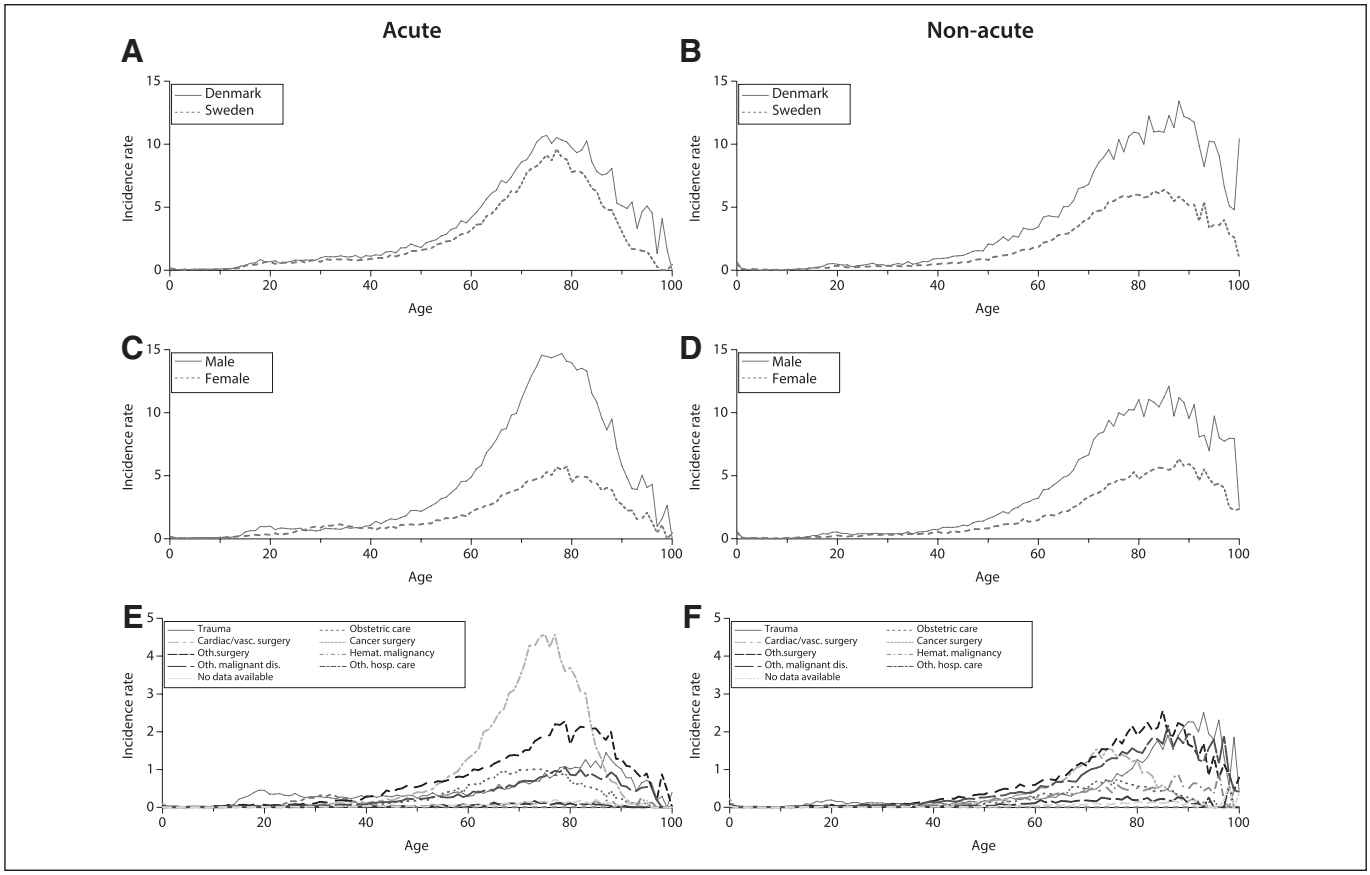

Figure 2. Incidence rates for massive transfusion per 10,000 person years, over age. **A**, Acute massive transfusion (≥ 10 RBC within 2 calendar days) for Sweden and Denmark. **B**, Nonacute massive transfusion (≥ 10 RBC within 7 calendar days) for Sweden and Denmark. **C**, Acute massive transfusion (≥ 10 RBC within 2 calendar days) for men and women. **D**, Nonacute massive transfusion (≥ 10 RBC within 7 calendar days) for men and women. **E**, Acute massive transfusion (≥ 10 RBC within 2 calendar days), stratified by indications (trauma, obstetric care, cardiac/vascular surgery, malignant surgery, other surgery, hematological malignancy, other malignant disease, other hospital care, no data available). **F**, Nonacute massive transfusion (≥ 10 RBC within 7 calendar days), stratified by indications (trauma, obstetric care, cardiac/vascular surgery, malignant surgery, other surgery, hematological malignancy, other malignant disease, other hospital care, no data available).

indication groups with the exceptions of trauma where there was a peak in young adults (age 19–20 yr) and for obstetric care with a peak around age 30.

Overall, the majority of massive transfusion episodes were acute, but with considerable variation between indication groups, ranging from 83.5% of all massive episodes in the obstetric group to 17.9% in the group of hematologic malignancy. The median number of transfused units (including all blood components) per episode was 19 (IQR, 14–29), decreasing with age from 23 U (IQR, 16–33) among patients younger than 18 years to 16 U (IQR, 12–22) among those older than 80 years. Men received slightly more units than women, 20 U (IQR, 14–30) versus 18 U (IQR, 14–27), respectively. The largest number of transfusions was seen among patients massively transfused for cardiac/vascular surgery with a median of 25 U (IQR, 18–36) and as many as 55.6% of the subjects in this group receiving 21–49 U. During the study period, 60.6% of all units were RBCs, 32.6% were plasma, and 6.2% were platelets. There was a slight increase in median plasma to RBC ratio over time (from 0.36 between 1996 and 2000 to 0.45 between 2006 and 2010). The highest plasma ratio was observed in the group "cardiac/vascular surgery," median ratio 0.6. In the trauma group, we saw a slight increase in plasma ratio over time, from 0.33 between 1996 and 2000 to 0.45 between 2006 and 2010. The median ratio of platelets was small, increasing from 0.00 in 1996–2000 to 0.06 in 2006–2010.

Table 2 presents 30-day mortality stratified by acute/nonacute. Overall, the 30-day mortality was higher in the acute group compared with the nonacute group (24.8% vs 21.0%). There were no marked changes over time, and in the recent time period, the overall 30-day mortality was 24.0%. There was a slightly higher mortality among male than female patients, 24.1% versus 21.6%. The highest 30-day mortality was observed for "other malignancies" (41.1%) and lowest for obstetric patients receiving massive transfusion (1.0%). The most extreme values were seen in the most recent time period, where "other malignancies" reached a 30-day mortality of 47.5% and the obstetric patients had a 30-day mortality of 0.7%. The 30-day mortality was higher in Denmark than in Sweden, 27.1% versus 20.8%. Finally, the 30-day mortality was higher among those transfused acutely on 1 calendar day, 29.3%, rather than on 2 calendar days, 24.8%.

Figure 3 presents the long-term survival for the different indication groups, stratified by acute and nonacute. There were

TABLE 2. Thirty-Day Mortality After Massive Transfusion Event

Number of Deaths/Total Number of Subjects	Acute	Nonacute
Overall, *n* (%)	13,336/53,836 (24.8)	8,017/38,221 (21.0)
Country, *n* (%)		
Sweden	7,954/35,356 (22.5)	4,044/22,232 (18.2)
Denmark	5,382/18,480 (29.1)	3,973/15,989 (24.9)
Age at transfusion, yr, *n* (%)		
< 18	149/775 (19.2)	107/584 (18.3)
18–39	636/5,569 (11.4)	282/2,602 (10.8)
40–64	3,532/17,166 (20.6)	2,323/11,482 (20.2)
65–79	6,313/22,820 (27.7)	3,449/15,442 (22.3)
80+	2,703/7,506 (36.0)	1,856/8,111 (22.9)
Indication for transfusion, *n* (%)		
Trauma	1,740/8,386 (20.7)	786/5,788 (13.6)
Obstetric care	13/1,408 (0.9)	3/278 (1.1)
Cardiac/vascular surgery	5,779/18,725 (30.9)	1,328/6,334 (21.0)
Cancer surgery	776/5,828 (13.3)	706/3,405 (20.7)
Other surgery	2,668/12,270 (21.7)	1,921/9,835 (19.5)
Hematological malignancy	241/676 (35.7)	796/3,096 (25.7)
Other malignant disease	249/607 (41.0)	522/1,269 (41.1)
Other hospital care	1,707/5,131 (33.3)	1,822/7,585 (24.0)
No data available	163/805 (20.2)	133/631 (21.1)

65,318 deaths over a median follow-up of 3.0 years (range, 0–26 yr). The early mortality was higher in the acute group, whereas the long-term mortality was higher in the nonacute group (**Fig. 3*A***). Mortality increased gradually with age. In patients aged 80 years or older, 74.4% (95% CI, 73.7–75.1) died within 5 years of the massive transfusion episode. Five-year mortality was higher in the age group 0–17 years, 28.3% (95% CI, 25.9–30.7), than in the age group 18–39 years, 20.4% (95% CI, 19.5–21.3) (**Fig. 3*B***). The long-term mortality differed considerably between the different indication groups, with a 5-year mortality of 90.1% (95% CI, 88.7–91.5) in the "other malignant disease," and a 5-year mortality of 1.7% (95% CI, 1.1–2.3) in the obstetric group (**Fig. 3*C***).

We also observed a pattern with a poorer survival for patients who received at least 50 U with a 5-year mortality of 61.2% (95% CI, 60.1–62.3) as compared with 54.3% (95% CI, 53.9–54.7) for patients who received 10–19 U. The differences in survival related to number of transfusions decreased with longer follow-up (**Fig. 3*D***).

Table 3 present SMRs over time since massive transfusion, both overall and stratified by indication. There was a common pattern with the SMRs, being notably high shortly after transfusion (within 6 mo), and then decreasing with time. Overall, the SMR was 26.2 (95% CI, 25.9–26.5) during the first 6 months after transfusion, decreasing to 1.6 (95% CI, 1.6–1.7) in the period 10 or more years after transfusion. The overall SMR was slightly higher in Denmark 30.9 (95% CI, 30.4–31.5) than in Sweden 23.5 (95% CI, 23.2–23.9). We also saw a marked sex difference, especially during the first 6 months, with SMRs of 33.8 (95% CI, 33.4–34.3) for men and 18.1 (95% CI, 17.7–18.4) for women. Once again the highest SMR, within 6 months of transfusion, was seen for the other malignant disease group (SMR, 82.8; 95% CI, 78.2–87.5) and the second highest for the obstetric care group (SMR, 60.0; 95% CI, 37.7–90.9).

DISCUSSION

Here, we present results from a large nationwide study describing the incidence of massive transfusion, the general characteristics of patients receiving massive transfusions, and the survival of these patients. Overall, we find a nonnegligible incidence of massive transfusions and a very high absolute mortality as well as high SMRs among the massively transfused patients. To our knowledge, no previous study has presented large-scale data on this patient group.

Our data show that the vast majority of massive transfusions are administered for major surgery (including cardiac/vascular, cancer, and other surgery). The overall 5-year mortality in massively transfused patients is very high, 54.6%, but

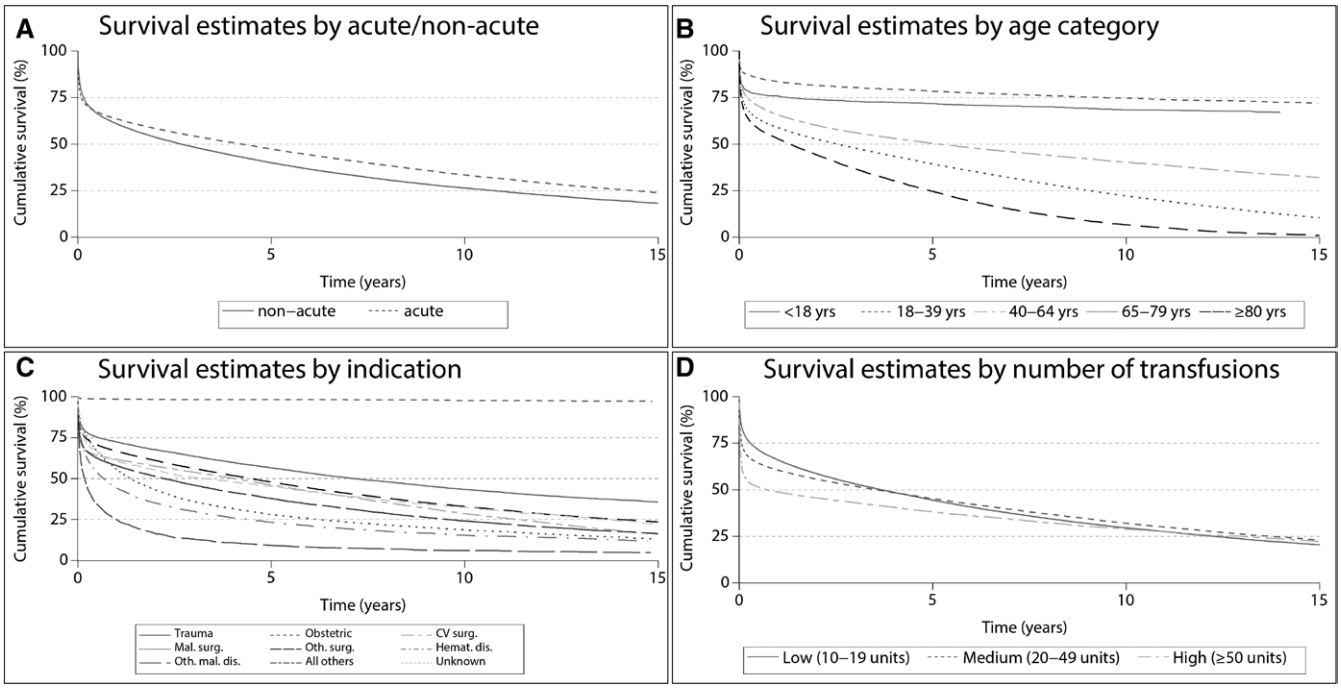

Figure 3. Kaplan-Meier survival proportions, over follow-up time 15 yr. **A**, For acute massive transfusion (≥ 10 RBC within 2 calendar days) and nonacute massive transfusion (≥ 10 RBC within calendar days). **B**, Stratified by age categories (< 18 yr, 18–39 yr, 40–64 yr, 65–79 yr, 80+ yr). **C**, Stratified by indications (trauma, obstetric care, cardiac/vascular surgery, malignant surgery, other surgery, hematological malignancy, other malignant disease, other hospital care, no data available). **D**, Stratified by number of blood components per episode (low, 10–19 blood components per episode; medium, 20–49 blood components per episode; high, 50+ blood components per episode).

the prognosis differed considerably between indications with the lowest mortality among patients massively transfused for obstetrical care where more than 98% were alive after 5 years, whereas only 9.9% were alive after 5 years when transfusion was associated with nonhematological malignant disease.

The key strength of this study is the use of large-scale databases with complete or near-complete coverage of all transfused patients in both countries, allowing analysis of underlying indications as well as unbiased long-term follow-up with little or no loss to follow-up. At the same time, it is possible that patients with missing or unknown identity at the time of the massive transfusion were not included in the analyses since they could not be traced when linkage was performed. While this implies that we may have underestimated the true incidence of massive transfusion, we believe that this error is unlikely to be considerable given that less than 2% of all transfusions in the relevant period were recorded to have been given to patients with unknown identity. One must also consider that the analyses were based entirely on registers which were not originally created for research purposes and that there has been a shift in coding practices during the study period (15). As such, it is comforting that we find relatively stable incidence rates over time, both overall and for the different indication groups, and we, therefore, speculate that such errors are unlikely to have had any large effects. That said, taking into account the coding imprecision, it is possible that the indication for some patients was misclassified, but we are confident that the general pattern is accurate.

Another limitation with the method used, is the lack of information regarding clinical data in the register. The available information is highly valid for descriptive analyses and information of general patterns, but we have chosen to not perform more detailed analyses regarding, for example, blood component ratios and survival, since such analyses require access to more detailed data on important confounders and transfusion data with better temporal resolution (16). In line with our purpose, we also chose a relatively broad classification of indications that could provide information on general characteristics without being prone to misclassification or biased results.

We used a nonstandard definition of massive transfusion compared to previous publications by distinguishing between acute and nonacute massive transfusions. Also, our definition of acute massive transfusion is less precise than the most common definition (3) as SCANDAT2 database only records calendar day and not exact time of transfusion. We, therefore, extended the time window to also capture patients who might have been admitted to hospitals during late hours. Naturally, this entails the inclusion of some patients who would not have been considered massively transfused in other studies. However, we consider this compromise to be appropriate as we would otherwise have missed relevant patients. Also, there is no international consensus regarding the definition of massive transfusion (4, 17) and the fact that we provide estimates using both 1-day and 2-day definitions, we are of the opinion that the provided estimates are still generalizable. When we performed the analysis with the more restrictive definition (≥ 10 red cell concentrates in 1 calendar day), similar results were obtained although there was a slightly higher 30-day mortality when using the more restricted definition. By

TABLE 3. Standardized Mortality Ratio, Presented by Time Since Transfusion

	Standardized Mortality Ratio (95% CI)				
	Time Since Transfusion				
	0–0.5 Yr	> 0.5–1 Yr	> 1–5 Yr	> 5–10 Yr	> 10 Yr
Overall	26.2 (25.9–26.5)	3.7 (3.7–4.0)	2.3 (2.2–2.3)	1.8 (1.8–1.9)	1.6 (1.6–1.7)
Country					
Sweden	23.5 (23.2–23.9)	3.7 (3.5–3.8)	2.1 (2.1–2.2)	1.7 (1.6–1.7)	1.5 (1.4–1.5)
Denmark	30.9 (30.4–31.5)	4.1 (3.9–4.3)	2.6 (2.5–2.7)	2.2 (2.1–2.3)	2.4 (2.2–2.5)
Sex					
Male	33.8 (33.4–34.3)	5.0 (4.8–5.2)	3.1 (3.0–3.1)	2.6 (2.6–2.7)	2.7 (2.6–2.8)
Female	18.1 (17.7–18.4)	2.7 (2.5–32.8)	1.5 (1.5–1.6)	1.2 (1.1–1.2)	1.0 (0.9–1.0)
Age at transfusion, yr					
< 18	928.1 (829.0–1,035.8)	49.5 (25.6–86.5)	43.5 (32.7–56.8)	21.1 (14.1–30.2)	11.1 (6.6–17.6)
18–39	458.3 (432.1–485.7)	61.4 (51.9–72.1)	19.9 (18.0–22.1)	10.4 (9.0–11.8)	5.5 (4.7–6.4)
40–64	115.0 (112.5–117.5)	19.5 (18.5–20.6)	8.4 (8.1–8.6)	4.3 (4.2–4.5)	3.0 (2.9–3.2)
65–79	33.2 (32.7–33.8)	4.5 (4.3–4.7)	2.6 (2.6–2.7)	2.0 (1.9–2.1)	1.5 (1.4–1.5)
≥ 80	9.9 (9.6–10.1)	1.4 (1.3–1.5)	1.1 (1.1–1.2)	1.0 (0.9–1.0)	0.6 (0.6–0.7)
Acute/nonacute					
Acute	32.6 (32.1–33.1)	4.0 (3.8–4.1)	2.3 (2.3–2.4)	1.9 (1.9–2.0)	1.7 (1.6–1.8)
Nonacute	20.5 (20.2–20.9)	3.7 (3.6–3.9)	2.2 (2.1–2.2)	1.7 (1.6–1.7)	1.5 (1.4–1.6)
Transfusion per episode, units					
10–19	16.6 (16.4–16.9)	3.4 (3.3–3.5)	2.1 (2.0–2.1)	1.6 (1.6–1.7)	1.4 (1.4–1.5)
20–49	41.3 (40.6–42.0)	4.6 (4.4–4.9)	2.6 (2.5–2.6)	2.1 (2.0–2.2)	1.9 (1.8–2.0)
≥ 50	108.2 (104.7–111.9)	6.3 (5.4–7.4)	3.5 (3.2–3.7)	2.7 (2.4–2.9)	2.4 (2.2–2.7)
Indication for transfusion					
Trauma	14.5 (14.1–15.0)	1.8 (1.6–2.0)	1.4 (1.3–1.5)	1.4 (1.3–1.4)	1.4 (1.3–1.6)
Obstetric care	60.0 (37.6–90.9)	5.3 (0.6–19.2)	1.6 (0.5–3.7)	1.4 (0.4–3.2)	1.6 (0.7–3.2)
Cardiac/vascular surgery	37.1 (36.3–37.9)	2.7 (2.5–3.0)	2.1 (2.1–2.2)	2.2 (2.1–2.2)	2.1 (2.0–2.2)
Cancer surgery	32.9 (31.8–34.1)	13.8 (13.0–14.7)	6.3 (6.0–6.5)	2.1 (2.0–2.3)	1.5 (1.3–1.7)
Other surgery	20.7 (20.2–21.2)	2.9 (2.7–3.1)	2.0 (1.9–2.0)	1.7 (1.6–1.8)	1.5 (1.4–1.6)
Hematologic malignancy	38.7 (36.9–40.6)	9.8 (8.7–10.9)	4.3 (4.0–4.6)	3.0 (2.6–3.4)	2.0 (1.6–2.6)
Other malignant disease	82.8 (78.2–87.5)	19.9 (17.0–23.0)	8.5 (7.6–9.6)	2.8 (2.0–3.6)	1.0 (0.6–1.5)
Other hospital care	25.4 (24.7–26.2)	3.2 (2.9–3.5)	2.3 (2.2–2.4)	1.8 (1.7–1.9)	1.3 (1.2–1.4)
No data available	24.3 (22.1–26.5)	4.2 (3.3–5.3)	1.7 (1.5–1.9)	1.4 (1.2–1.6)	1.2 (1.0–1.4)

introducing the definition of nonacute massive transfusion, we also included patients who received at least 10 erythrocyte units over a maximum of 7 days, since this patient group arguably is as interesting from the perspective of transfusion-associated risks.

There is a current consensus on the importance of increasing the ratio of plasma and platelets, respectively, to RBC in massive transfusions (18, 19). Recently, a randomized control trial was completed showing a trend toward better survival when comparing high to low ratios of plasma and platelets to red cells, however failing in generating significant differences on the primary outcome (20). In this study, we observed a low plasma and platelet use among the massively transfused patients. However, our data are to some extent historical, since the first international consensus was established in only 2004, and with time, our data show a trend toward increased plasma

and platelet use, indicating an increasing adherence with the current consensus.

The higher incidence of massive transfusion in Denmark, compared with Sweden, in recent years, is described previously (12) and is assumed to be partly due to different therapeutic traditions in the two countries. This difference does not seem to be attributable to a certain indication group since the incidence is consistently different between the two countries for most indications.

The general assumption is that the main indications for massive transfusion are trauma, obstetrical bleeding, major surgery, and gastrointestinal bleeding (9, 10). In contrast, our study reveals that massive transfusion for obstetrical care is in fact quite uncommon and that traumas similarly account for a small proportion of all massive transfusions. Major surgery, including cardiac/vascular surgery and cancer surgery, and other types of surgery dominate in our dataset. In fact, among transfused trauma and obstetrical patients, massive transfusion is less frequent than in transfused patients undergoing most other types of surgery. Given the stability over calendar time and the similar pattern in the two countries, as well as when the time frame for "acute massive transfusion" was shortened to 1 calendar day, we believe it is likely that similar patterns would be found also in other high-resource countries. Smaller differences in practices between countries most probably do not have a greater impact on the distribution on indication since massive transfusion is a treatment only used in emergency situations where local treatment cultures is of lesser importance. However, there might be some smaller differences between countries regarding trauma as the reported incidence and type of injuries slightly vary (21).

Overall, we observed a very high mortality, both on an absolute and a relative scale. As expected, however, there was considerable variation in both short- and long-term mortality between the different indication groups. In this analysis, the obstetric patients stood out by having a very low absolute mortality. At the same time, relative to the background population, the mortality in this patient group was strikingly elevated early in the follow-up, reflecting a low expected mortality in young women. At the opposite end of the spectrum, patients who were transfused for malignant disease without undergoing surgery had a 9.9% five-year survival which was coupled by a sustained high SMR. A similar pattern, albeit less extreme, was seen for patients who were massively transfused for cancer surgery.

The short-term mortality dominates in our results, and for the most part, the high SMRs that were observed during the first 6 months decreased with time. Intriguingly, the SMRs remained elevated for more than 10 years after the first massive transfusion for almost all indication groups, which illustrates the importance of the indication as a determinant of long-term prognosis. Also, elevated SMRs throughout the time period were noted in all age categories with exception for those patients 80 years or older at transfusion. In this group, we observed SMRs below 1.0 with long-term follow-up. We speculate that this might be due to indication bias where very frail elderly patients would not receive aggressive treatment, resulting in a better survival than in an equally old background population. As in a previous study of the transfused population in Sweden and Denmark (22), we observed both a higher short- and long-term mortality in Denmark compared with Sweden. We lack an exhaustive explanation for this difference, but note that a higher mortality in Denmark than in Sweden is a general phenomenon, not limited only to massively transfused patients, and it is generally ascribed to a higher level of tobacco smoking and alcohol consumption in Denmark (23). As we did not study any such factors or other comorbidities in this study, we can only speculate in whether it might be influencing factors also in our material. The correlation between mortality and number of blood components per episode is also in line with previous observations (22). It seems that the excess mortality in the patients who received the largest number of transfusions was most pronounced in the early follow-up period, but in fact, the excess mortality persisted throughout follow-up. Also, a higher mortality with increasing age and for men compared with women was observed. Strikingly, among the oldest massively transfused patients, only 26% were alive after 5 years, which seems in line with the data presented by Mitra et al (24) who reported 30% in-hospital mortality for trauma patients aged 65 years or older who received at least one blood transfusion.

CONCLUSION

In conclusion, this is the first large-scale study describing the complete spectrum of massive transfusions. We report that major surgery is the leading indication for massive transfusion, while trauma and obstetric indications constitute a relatively small part. We also report a nonnegligible incidence and a very high mortality. Our results provide a comprehensive background on massive transfusions and show a slightly different picture than the one most commonly referred to. Although there has been rapid improvement in the management of hemorrhaging trauma patients, the unexpectedly wide range of indications that are massively transfused serve to highlight the paucity of data on how to manage other patient groups who require large numbers of transfusion. As such, we are of the opinion that the knowledge of indication patterns should be of wide interest and can serve as a more comprehensive background when choosing patient groups for possible studies in the future.

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