# Transfusion use in patients with myelodysplastic syndromes (MDS): a nationwide, retrospective cohort study

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## Background

It is well known that a significant fraction of all manufactured blood components are allocated to patients with hematological or oncological diseases. This is the case for all types of blood components, but especially so for platelet concentrates where as many as 30-50% of blood units are used for patients undergoing chemotherapy.[1]

In the scope of the ongoing SCANDAT (Scandinavian donations and transfusions) project we have access to detailed data on all blood transfusions administered in Sweden and Denmark in the past two decades. These data have been linked with a range national health outcomes registers, including cancer and hospital care, which allows the characterization of transfusion patterns for various patient populations.[1] Using these data we have recently performed a broad characterization of blood use in patients with hematologic disease. In this study we demonstrate that young patients with MDS receive blood transfusions with a corresponding direct material cost close to $25,000 only in the first year of therapy. As such, total costs for transfusion therapy are thus likely close to, or over, $50,000 per patient per year for this patient group. However, the available data did not allow stratification by MDS risk group.[2]

Because indications for transfusion and their frequency will likely differ considerably between low-intermediate- and high-risk MDS patients, we propose a more refined analysis with the overarching aim of providing a more detailed and contemporary understanding of blood use and associated costs for patients with MDS, with emphasis on characterizing differences according to diagnostic (WHO) or prognostic (IPSS/IPSS-R) risk groups. This data may then be used to provide a more nuanced cost analysis for emerging MDS treatments that may be viable therapeutic alternatives to transfusion therapy.

## Specific aims

The overarching aim with the proposed research is to perform a detailed characterization of transfusion use for patients with myelodysplastic syndromes.

Specifically we will:

- The primary aim is to provide a detailed and contemporary understanding of RBC transfusion use for patients with MDS in Sweden, stratified by MDS diagnostic and prognostic group (IPSS and WHO risk groups) age and therapy (exploratory). Specifically, we will compute expected number of transfusions, by type.
- The secondary aim is to compute ensuing costs for transfusion therapy, including both direct material costs (based on well-known costs for different types of blood components) as well as estimated indirect transfusion costs, which will include also expected costs for cross-matching, ordering, transfusing, and other related costs.

## Approach

### Data sources

To allow more detailed analyses of blood use in patients with myelodysplastic syndromes, we now propose to add data from the Swedish National MDS Register to the SCANDAT database. Record linkages will performed using national registration numbers (NRNs) assigned to all persons living in Sweden, and which are used in all relevant registers. Data available in the MDS register will allow more detailed analyses, both with regards to different disease characteristics groups, but also by incorporating limited data on treatment. Furthermore, by linking the SCANDAT database with the Swedish prescription drug register we will be able to identify and incorporate costs for transfusion-associated treatments, e.g. iron chelation.

### Study design

Analyses will be based on a cohort of all patients diagnosed with MDS and registered in the Swedish MDS register between 2008 and 2018. Patients will be followed from their diagnosis until their death or emigration. In sensitivity analyses we will also censor from further follow-up upon allogenic bone marrow transplantation. Transfusions will be tracked using the SCANDAT database, which is nationally complete in Sweden since the mid 1990's, for both in- and outpatient transfusions.

## Inclusion and exclusion criteria

The study will include all adult patients with a confirmed histopathological diagnosis of MDS in the time period from 2008-2018, living in Sweden. There will be no specific exclusion criteria, but in analyses stratified by diagnostic or prognostic subgroups, we will restrict the analyses to patients with known WHO-subgroup and IPSS/IPSS-R risk group respectively.

## Statistical analyses

The analyses will be based on all patients with an MDS diagnosis. The bulk of analyses will be performed using descriptive statistical methods, i.e. means and medians, with accompanying measures of uncertainty. All estimates will be presented both overall and stratified by disease risk group (IPSS or IPSS-R, as applicable) and/or disease group (WHO).

Recognizing that patients with MDS have a very high mortality we will also perform analyses where the main variables of interest (i.e. transfusion frequency and associated costs) are adjusted for patient survival. We have previously applied a method where we first compute a cumulative number of transfusions per patient as a function of time since diagnosis and then calculate a cumulative average number of transfusions by dividing this number of the corresponding number of patients who remain alive and under follow-up at the same time.[2] Using this adjusted model, we can derive blood utilization estimates which incorporate both mortality, cure following aggressive treatment such as transplantation, as well as transition between risk groups. Estimates will thus be more specific for the subgroup at hand. Confidence intervals for averages can be constructed using boot strap methods.[3]

Average ensuing costs can be directly computed from average number of transfusions by multiplying with per-unit cost estimates. For the latter, the main analyses will performed looking only at known direct costs (derived using known costs for blood units, made publicly available by Swedish county councils). In addition, we will also attempt to estimate total costs, by incorporating also indirect costs, e.g. infusion costs, patient blood testing, nurse time, iron chelation. These supplementary analyses will be based on clinically derived scenarios, accounting for blood testing frequency, setting for transfusion, etc. Using these data we will compute a credible cost interval for the total cost.

Analyses will be performed using the SAS statistical analysis software, version 9.4.

## Power analysis

The study will be based on all patients diagnosed with MDS in Sweden during a 9-year period. Considering that approximately 300-350 patients are registered in the MDS register annually, we expect to include more than 3000 patients, in total. Of these, close to 100% will have received at least one blood transfusion, with an expected average of 30 red-cell units and 15 platelet concentrates during only the first year of therapy. For the overall analyses we will thus have excellent statistical power. In analyses stratified by risk group, etc., the statistical precision will be lower, but adequate even for analyses restricted to <5% of the population. Specifically, at an alpha level of 0.05 and an expected number of red-cell transfusions of 30, we expect a 95% confidence limit from 28.5 to 31.5, which should be sufficient for most purposes.

## Safety reporting

No data on adverse reactions will be collected or recorded due to the retrospective and observational study design.

## Data collection and analysis plan

- All necessary data on transfusion patterns have been collected and are complete through mid-2018
- Linkage with population registers, as well as with the national MDS register will be completed during the summer of 2019
- Data cleaning, harmonization and preparation will be performed early fall 2019
- Data analyses will be performed during the fall of 2019
- After data collection is completed, a scientific manuscript and final report will be prepared, tentatively during the beginning of 2020
- The final report is expected to be finished no later than June 30, 2020.

## References


1. Edgren G, Rostgaard K, Vasan SK, et al. The new Scandinavian Donations and Transfusions database (SCANDAT2): a blood safety resource with added versatility. *Transfusion.* 2015;55(7):1600-1606.
2. Zhao J, Ryden J, Wikman A, et al. Blood use in hematologic malignancies: a nationwide overview in Sweden between 2000 and 2010. *Transfusion.* 2018;58(2):390-401.
3. Jiang H, Zhou XH. Bootstrap confidence intervals for medical costs with censored observations. *Stat Med.* 2004;23(21):3365-3376.



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