Automating outcome analysis after stem cell transplantation: the YORT tool

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ARTICLE

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Automating outcome analysis after stem cell transplantation: The YORT tool

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Hematopoietic stem cell transplantation is a high-risk procedure. Auditing and yearly outcome reviews help keep optimal quality of care and come with increased survival, but also has significant recurring costs. When data has been entered in a standardized registry, outcome analyses can be automated, which reduces work and increases standardization of performed analyses. To achieve this, we created the Yearly Outcome Review Tool (YORT), an offline, graphical tool that gets data from a single center EBMT registry export, allows the user to define filters and groups, and performs standardized analyses for overall survival, event-free survival, engraftment, relapse rate and non-relapse mortality, complications including acute and chronic Graft vs Host Disease (GvHD), and data completeness. YORT allows users to export data as analyzed to allow you to check data and perform manual analyses. We show the use of this tool on a two-year single-center pediatric cohort, demonstrating how the results for both overall and event-free survival and engraftment can be visualized. The current work demonstrates that using registry data, standardized tools can be made to analyze this data, which allows users to perform outcome reviews for local and accreditation purposes graphically with minimal effort, and help perform detailed standardized analyses. The tool is extensible to be able to accommodate future changes in outcome review and center-specific extensions.

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INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is a potentially curative procedure for a variety of malignant and non-malignant indications [1]. It comes with considerable risk, which makes quality management essential. When judging quality of HSCT care, multiple factors are relevant, including overall survival, relapse of disease, engraftment and graft failure, acute and chronic graft vs host disease (GvHD), treatment complications, viral reactivations, and other infections.

To ensure quality of care in HSCT, accreditation standards and quality management systems are used, which require periodic analysis of outcome, auditing, and entry of data in a central registry [2]. This leads to improved quality of care, which may improve survival after HSCT in accredited centres [3–5]. However, investing in accreditation comes with significant recurring costs [6], which is especially relevant for low- and middle-income countries [7].

Since both data entry and periodic analysis are standardized, parts of these analyses could be automated. By automating the analysis, time and effort can be saved, while increasing reproducibility. In addition, due to the reduced effort of performing this analysis, it could be easier to extend the analyses with more comparisons, such as between donor type and graft source, and versus longer, historic cohorts.

To automate the analysis, R, a freely available open-source language software environment for statistical computation, is a good candidate [8]. R is often challenging to use, since it relies on the user to write commands. Earlier work to make R easier to use when analysing HSCT results has led to EZR, a software product which adds a graphical interface for common analyses, but retrieving the data, ensuring it is in the right format to be analysed, choosing which analyses to perform, and performing them was still left up to the user [9].

We aimed to improve outcome analyses by creating an easy-to-use, graphical tool, that works directly with data in the format of the Registry of the European Society for Blood and Marrow Transplantation (EBMT) without requiring data manipulation. This tool allows users to define a patient population and groups to compare within it, and performs standardized analyses comparing those groups, which minimizes the effort and knowledge required to review and compare outcome.

METHODS

To provide these automated analyses, we created the Yearly Outcome Review Tool (YORT), a standalone software tool. It is built upon R and Shiny, an R web application framework [10]. The tool imports a centre-specific backup-type export of the EBMT registry, and performs analyses on demographics, engraftment, survival and event-free survival, complications, and data completeness. It transparently reports on missing data to allow users to inspect and correct the data as it is analysed.

YORT allows the user to define filters, for example, to only analyse a specific year or specific diagnosis, and groups, for example, to compare

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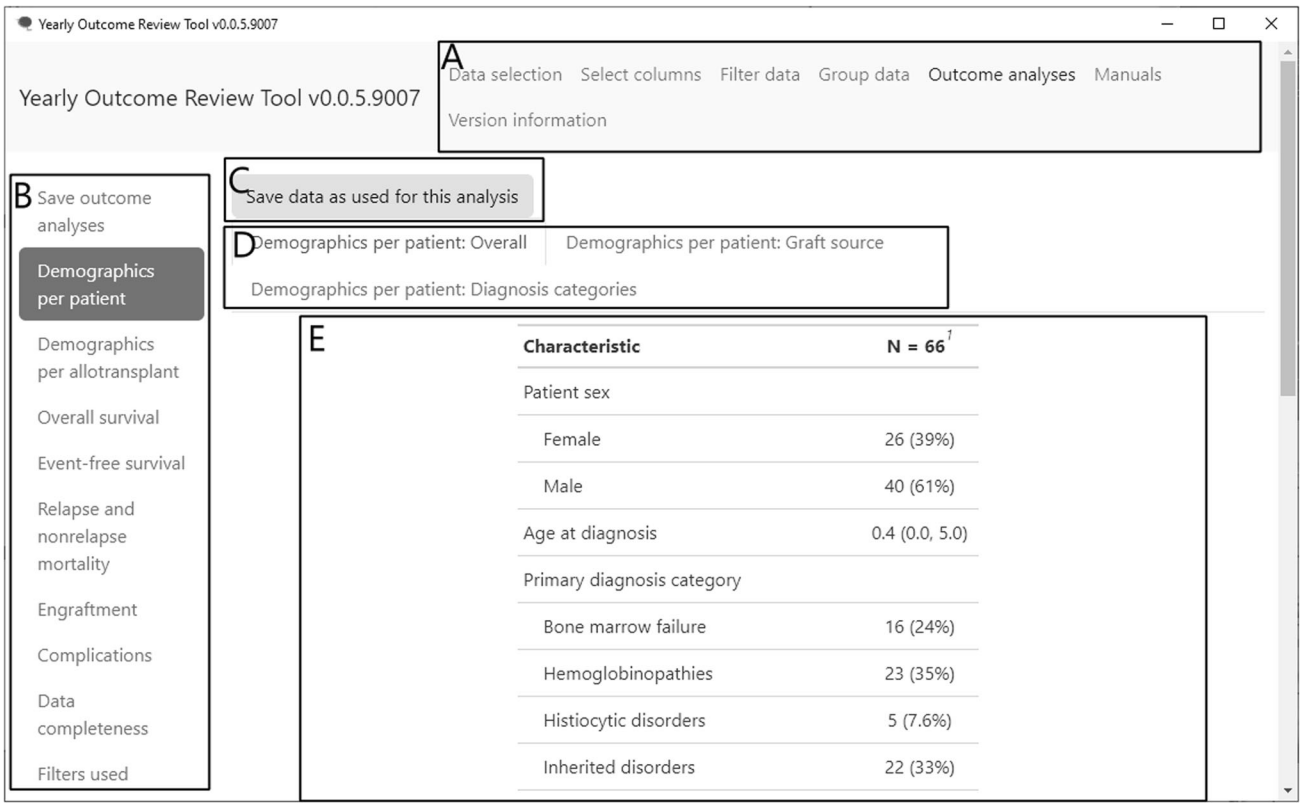

Fig. 1 Graphical user inteface for YORT. A The main application tabs, corresponding to main modules, currently the outcome analyses module is open. **B** The subtabs, most main modules have multiple subtabs. For the outcome analyses module, each subtab corresponds to an outcome module performing a single outcome analysis, except for the first, that allows saving of all outcome analyses. **C** The download data button, which allows users to download the data as-used for a certain outcome analysis, optionally including groups. **D** The outcome tabs, one for the ungrouped result, and then one for each group with an analysis corresponding to that group. **E** The outcome analysis body, containing tables and graphs for the current analysis.

stem cell source, disease and donor type, or one period versus another. Predefined filters and groups are offered as examples, which can be added with a single click, and then edited when required. Filters exclude patients, transplants, complications, or other data, while groups are used to compare data. By default, for each table in the registry, only columns commonly used are visible to define groups and filters, however, users can define filters and groups using all data in the registry. Filters and groups can be saved and shared for reproducibility.

All analyses in the tool are performed according to EBMT recommendations [11]. For survival and event-free survival, differences are plotted using Kaplan-Meier curves and tested using a log-rank test, and survival percentages at 100 days, 6 months, 1 and 2 years and last timepoint included are reported. The unadjusted death counts are also reported, including cause of death as entered in the registry. For engraftment, relapse rate and non-relapse mortality, competing risk cumulative incidence graphs are reported, and tested using Gray's Test, with percentages at relevant timepoints. For demographics, comparisons are done using a Chi-squared test for categorical data with no more than 5 categories, or a Kruskal-Wallis test for continuous data.

For each analysis, the tool provides a download button that provides the file(s) exactly as used in the analysis, in either SPSS (.sav), CSV, or Excel (.xlsx) format, including UPNs, to allow the user to track down missing and unexpected data. The analyses can be saved, and a stepwise visualization of the defined filters can be included for reproducibility.

YORT is available on Windows, since the EBMT registry exports to Microsoft Access, a Windows-exclusive program. It is both installable as a standalone program, in which case all dependencies, including R, are bundled together into an Electron application [12], and as an R package, which allows users familiar with R easy access to the tool, including the ability to extend it without modifying the source code. Detailed manuals on how to use the tool are integrated in it.

The tool is released on Zenodo under https://doi.org/10.5281/zenodo.7318445 [13], and includes an updater that will alert users when a new version is available, to make sure users know if they are using the most recent version, allowing us to keep the tool up-to-date and incorporate changes in the future, for example, to accommodate changes in the data files or additional analyses.

A key consideration for the tool was extensibility, which is realised by working with modules, and allowing modules to be added or swapped using the R package without modifying the tool itself. Modules come in two flavours: outcome analysis modules, which provide a single analysis to be performed on the filtered data both with and without groups, and core modules, which provide core functionality to the tool. Outcome modules can be developed only with knowledge on R and the structure of the EBMT registry and require minimal knowledge on Shiny or how the tool works, while core modules do require knowledge on Shiny. The tool comes with manuals and examples on how to develop these modules, and with instructions on how to create a new installer with custom modules added to it.

The graphical interface is structured in the following way: At the top, we can switch between the main modules: data selection, column selection, filters, groups, and the analyses (Fig. 1A). We also have manuals directly available to us. When no data has been imported yet, only the data selection pane and the manuals are available (including a manual on how to prepare an export in the right format). Within most modules, at the left, there is a further selection, between filters, groups, and analyses (Fig. 1B). When displaying an analysis, we can choose to download the data (Fig. 1C), between the overall analysis and to compare groups (Fig. 1D) and view the analysis content (Fig. 1E). When the tool is calculating, a busy indicator is shown at the top right.

RESULTS

Example analysis

To demonstrate YORT, we performed an analysis where we filtered on the first allogeneic transplant for patients with an age below 18 at time of transplant, performed between 2019 and 2021 at the

Table 1. A: Demographics per patient. B: Demographics per transplant.

A: Demographics per patient.					
Characteristic	***N* = 66**	**BM, *N* = 54**	**PB, *N* = 1**	**CB, *N* = 11**	***p*-value**
Patient sex					0.5
Female	26 (39%)	23 (43%)	0 (0%)	3 (27%)	
Male	40 (61%)	31 (57%)	1 (100%)	8 (73%)	
Age at diagnosis	0.4 (0.0, 5.0)	0.7 (0.0–17.3)	1.2 (1.2–1.2)	0.2 (0.0–17.3)	0.6
Primary diagnosis category					0.004
Bone marrow failure	16 (24%)	15 (28%)	0 (0%)	1 (9.1%)	
Hemoglobinopathies	23 (35%)	21 (39%)	0 (0%)	2 (18%)	
Histiocytic disorders	5 (7.6%)	1 (1.9%)	0 (0%)	4 (36%)	
Inherited disorders	22 (33%)	17 (31%)	1 (100%)	4 (36%)	
Primary diagnosis					
Bone marrow failure: Acquired	12 (18%)	11 (20%)	0 (0%)	1 (9.1%)	
Bone marrow failure: Congenital	4 (6.1%)	4 (7.4%)	0 (0%)	0 (0%)	
FELH / FHLH	5 (7.6%)	1 (1.9%)	0 (0%)	4 (36%)	
Hemoglobinopathy	23 (35%)	21 (39%)	0 (0%)	2 (18%)	
Inherited disorder	1 (1.5%)	1 (1.9%)	0 (0%)	0 (0%)	
Primary immune deficiency	21 (32%)	16 (30%)	1 (100%)	4 (36%)	
Number of stem cell transplants					0.001
1	61 (92%)	50 (93%)	0 (0%)	11 (100%)	
2	5 (7.6%)	4 (7.4%)	1 (100%)	0 (0%)	
Age at first HSCT	7.8 (1.7, 13.8)	10.1 (0.2–17.7)	2.2 (2.2–2.2)	0.5 (0.2–17.5)	0.02
B: Demographics per transplant.					
Multiple donors					
No	66 (100%)	54 (100%)	1 (100%)	11 (100%)	
Preparative (conditioning) treatment					
Yes	66 (100%)	54 (100%)	1 (100%)	11 (100%)	
Regimen intended to be myeloablative *(full intensity)*					< 0.001
No	2 (3.0%)	0 (0%)	1 (100%)	1 (9.1%)	
Yes	64 (97%)	54 (100%)	0 (0%)	10 (91%)	
TBI					
No	66 (100%)	54 (100%)	1 (100%)	11 (100%)	
TLI / TNI / TAI					
No	66 (100%)	54 (100%)	1 (100%)	11 (100%)	
GvHD prevention in the patient					
Yes	66 (100%)	54 (100%)	1 (100%)	11 (100%)	
Patient age	7.8 (0.2–17.7)	10.1 (0.2–17.7)	2.2 (2.2–2.2)	0.5 (0.2–17.5)	0.02
CMV match (patient/donor)					0.3
−/−	13 (20%)	11 (20%)	0 (0%)	2 (18%)	
−/+	7 (11%)	6 (11%)	0 (0%)	1 (9.1%)	
+/−	12 (18%)	7 (13%)	0 (0%)	5 (45%)	
+/+	34 (52%)	30 (56%)	1 (100%)	3 (27%)	
EBV match (patient/donor)					> 0.9
−/−	7 (12%)	7 (13%)	0 (0%)	0 (0%)	
−/+	13 (23%)	13 (24%)	0 (0%)	0 (0%)	
+/−	3 (5.3%)	3 (5.6%)	0 (0%)	0 (0%)	
+/+	34 (60%)	31 (57%)	1 (100%)	2 (100%)	
Unknown	9	0	0	9	
Donor relation					> 0.9
Identical sibling	16 (24%)	14 (26%)	0 (0%)	2 (18%)	
Matched other relative	2 (3.0%)	2 (3.7%)	0 (0%)	0 (0%)	

Table 1. continued

B: Demographics per transplant.					
Mismatched relative	1 (1.5%)	1 (1.9%)	0 (0%)	0 (0%)	
Unrelated	47 (71%)	37 (69%)	1 (100%)	9 (82%)	
Donor age	22 (0−48)	24 (5−48)	38 (38−38)	0 (0−0)	< 0.001
Conditioning					0.094
Alemtuzumab, Fludarabine, Thiotepa, Treosulfan	11 (17%)	8 (15%)	0 (0%)	3 (27%)	
Alemtuzumab, Fludarabine, Treosulfan	8 (12%)	4 (7.4%)	1 (100%)	3 (27%)	
ATG, Cyclophosphamide, Fludarabine	12 (18%)	11 (20%)	0 (0%)	1 (9.1%)	
ATG, Fludarabine, Thiotepa, Treosulfan	28 (42%)	26 (48%)	0 (0%)	2 (18%)	
ATG, Fludarabine, Treosulfan	3 (4.5%)	3 (5.6%)	0 (0%)	0 (0%)	
Dexamethasone, Fludarabine, Thiotepa, Treosulfan	1 (1.5%)	0 (0%)	0 (0%)	1 (9.1%)	
Fludarabine, Thiotepa, Treosulfan	1 (1.5%)	0 (0%)	0 (0%)	1 (9.1%)	
Fludarabine, Treosulfan	2 (3.0%)	2 (3.7%)	0 (0%)	0 (0%)	

A. Demographics per patient as reported by the tool, both overall and per graft source (combined from separate tabs, shortened). B. Demographics per allogeneic transplant as reported by the tool (shortened, medication names shortened, brand names removed). Both missing and unknown data is reported as Unknown.

Leiden University Medical Centre, and grouped by graft source and main diagnosis categories. A video of how this analysis was performed, including all steps required to reproduce the analysis, is included in the video abstract (1:47 to 3:23). Figures and tables are taken directly from the tool, and only edited to resize, shorten, and panel them.

The full export file generated by the tool has been included as supplemental file A. This file does not include the analyses on complications due to possibly identifying information, relapse rate and non-relapse mortality since this cohort only consisted of non-malignant diagnoses, data completeness and filtering steps since they lack scientific relevance.

The demographics are split in two tables, those per patient (Table 1A) and those per transplant (Table 1B). A total of 66 patients were included. 26 patients were transplanted for a primary immunodeficiency, 23 were transplanted for a hemoglobinopathy, 16 for bone marrow failure, and 1 for Glanzmann thrombasthenia. Diagnosis and graft source were related, with 80% of the 5 HLH patients receiving a cord blood graft, while in all other categories bone marrow grafts were most common ($p = 0.004$).

Overall survival at 100 days was 94%, and this explains in part the difference between the two ways of analysing engraftment. At 1-year, overall survival was 92%, and there were no deaths after 1 year. Survival between diagnoses did not differ significantly, though trends were in line with literature, with the lowest 2-year survival (80%) histiocytic disorders, 86% 2-year survival in inherited disorders, 96% in hemoglobinopathies, and no deaths in the 16 included bone marrow failure patients (Fig. 2a, b). Survival did not differ between graft sources used.

Event-free survival (EFS), defined as survival without relapse, disease progression, subsequent transplant, or stem cell boost was 92% (86–99%) at 100 days, 86% (78–95%) at 1 year, and 77% (63–94%) at three years, with events being death in 5 patients, subsequent transplants in 5, and a boost in 1 patient (Fig. 2c). Event free survival did not differ between the graft sources used.

Neutrophil engraftment (neutrophils $> 0.5 \times 10^9$/L after stem cell transplant) was reached for 95% of patients, while this was 91% for platelet engraftment above 50×10^9/L (Fig. 2d). Using survival analysis and censoring on death and second transplant, engraftment of neutrophils was 86% at 30 days and 98% at 100 days, and engraftment of platelets was 61% at 30 and 95% at 100 days. Engraftment of thrombocytes appeared slower when using a cord blood graft (27% at 30 days, vs 68% for a bone marrow graft), however, this was not significantly different ($p = 0.082$).

Acute GvHD occurred in a total of 17 patients, out of which 4 experienced grade III-IV GvHD. Chronic GvHD occurred in 4 patients, out of which it was extensive in 3. No *P*-values are shown for GvHD, infections and non-infectious complications in the tool, since to do so choices need to be made on handling competing risks and incomplete follow-up.

Testing and validation

YORT was distributed to a total of 5 HSCT centres accredited according to the 'JACIE' system (Joint Accreditation Committee of the International Society of Cellular Therapy, ISCT, and EBMT) in three different countries for initial testing, and feedback was incorporated into the tool. Security was assessed through a Security Impact Analysis (supplemental file B text 1). The tool was presented to the EBMT executive committee, who evaluated to tool and acknowledged its value and usefulness for the purpose of quality management and made a statement confirming its usefulness (supplemental file B text 2).

DISCUSSION

This article presents YORT, a tool that can make detailed analyses on outcome of HSCT for individual centres based on the standardized export the EBMT registry offers. These analyses are primarily intended to aid with quality management and yearly outcome reviews by making it easier to perform standardized analyses. The ability to use groups and filters allows for easy comparison between historic cohorts, between different donor types or treatments, or other variables relevant for quality of care.

A key challenge when developing the tool was to make it easily extensible, to accommodate future analyses and custom analyses per centre. We have addressed this by using a modular approach, which allows statisticians with little experience in application development to add custom analyses to the tool. This could prove valuable as JACIE moves towards including patient-reported outcome and extending quality management to posttransplant care [14], increasing the need for more complex analyses integrating patient experience with morbidity and mortality.

The extensibility could be of use as the spectrum of new cellular therapies, including genetically modified cells, is steadily expanding. As standards develop on how to analyse outcome for these therapies, they can be incorporated as a module, and once they

are fully accepted, that module can be added into the tool. The ability to easily extend the tool without modifying its source code democratizes its development, as independently developed additions can be made without conflicting with future updates of the tool, and these additions can be incorporated into the tool if they are deemed to be useful to most users.

Privacy and data security was critical to make the tool generally usable. The tool only connects to the internet to check for updates, and does not share or import any data. We could achieve this, since the tool operates on a local export file, and not the registry itself. It does not report usage or crash reports back to the developer. This was key to make sure the tool can be used as any statistical application can, without data sharing or processing agreements. While the tool could easily be made available as a web service as it is built on web technology, this is not recommended.

The tool offers a straightforward way to inspect data completeness on aspects relevant for the analyses, such as survival, engraftment, and adequate length of follow-up. However, we believe that increasing data usefulness to the institutions collecting the data is the primary way to increase data quality. If exported EBMT registry data is directly used for quality management purposes in a standardized way, deficiencies that inhibit the use of this data for assessment of outcome will become known, and as the data is used directly, the easiest way to solve these deficiencies is to correct them in the registry. We hope this approach will lead to a substantial increase in registry data quality, both helping the individual centre with future analyses and increasing the accuracy of future EBMT studies.

The ability to export and share groups and filters on a standardized dataset has many use cases. For example, when unexpected outcome is seen in a subgroup of patients, a centre could provide a filter identifying this subgroup to other centres, to easily detect patterns in outcome. An investigator of a retrospective study might also develop a filter for patients meeting the inclusion criteria, after which other centres can run an analysis with that filter to identify possible inclusions and assess outcome and data completeness for those patients. An investigator could even develop a custom outcome module to perform custom data checks and aid in creating data exports. However, the analyses reported by the tool are not intended for use in scientific hypothesis testing, as many tests are performed without multiple testing correction, and all analyses are univariate.

Existing efforts to provide automated outcome reports after stem cell transplants do exist, such as the Japanese TRUMP2 system, which provides scripts for R and Stata to analyse registry results [15]. National registries and benchmarking efforts also commonly provide periodic reports [16]. Novel aspects of this tool include that it allows users to perform analyses at will using a graphical interface, defining patient population and comparisons through graphically defined filters and groups, and providing detailed outcome including engraftment, EFS and complications.

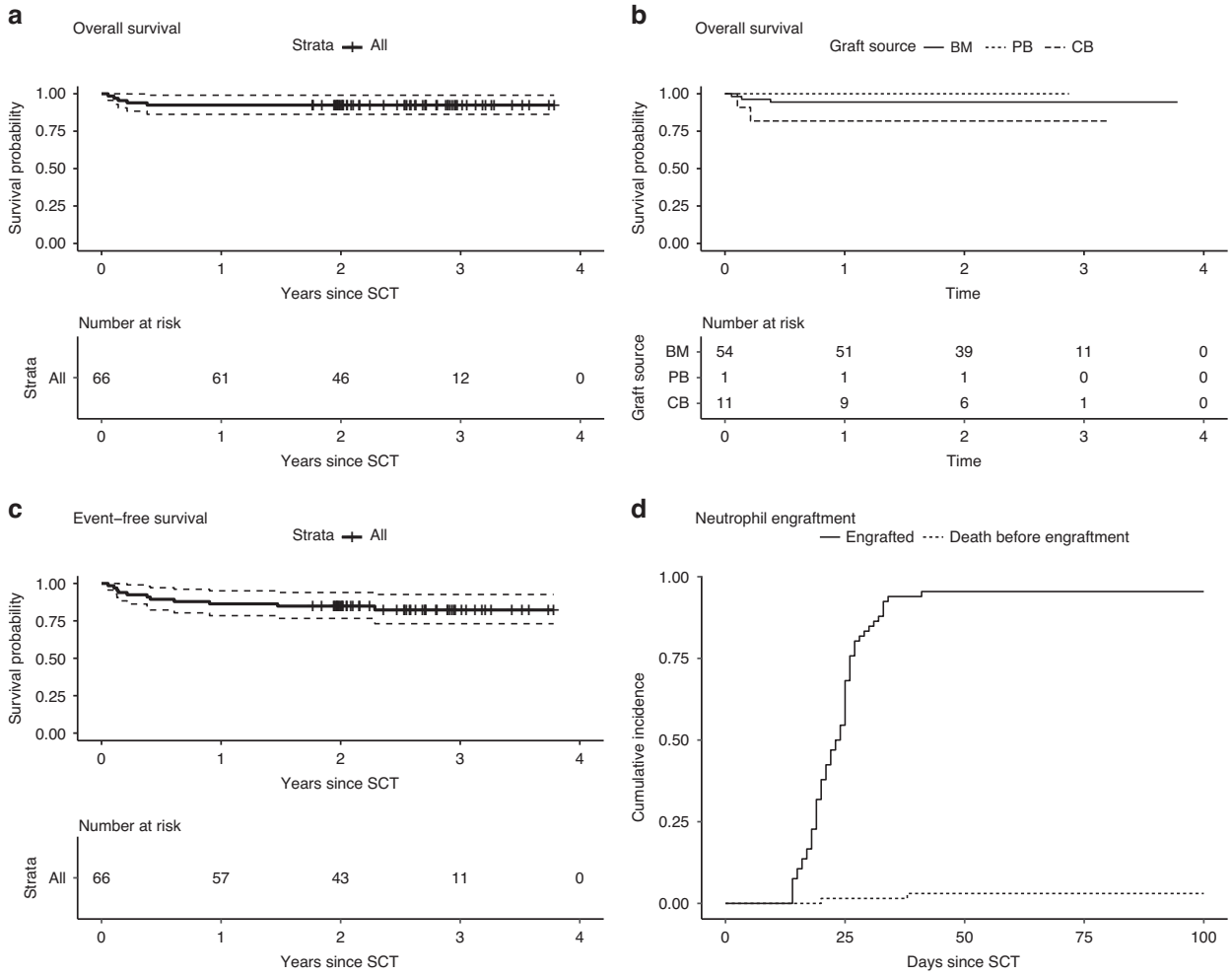

Fig. 2 Survival outcomes as reported by YORT. a Overall survival for all patients. **b** Overall survival, split by diagnosis categories as defined in the EBMT registry. **c** Event-free survival, including subsequent transplants, boosts and relapse as events. **d** Neutrophil engraftment, using a threshold value of $0.5 * 10^9$ cells/L, as defined in the EBMT registry.

It is both installable as a standalone offline program for users unfamiliar with statistical programming languages, as well as useable and extensible within R, while existing efforts either provide a static file, or a script for users with statistical expertise.

Comparing with conventional statistical applications such as SPSS and Stata, the main difference is that this tool is programmed to know how data is entered and how to analyse the data. This allows for easy analysis, while standardising the analyses performed, reducing the chance of errors. It also directly uses a hierarchical database export, while statistical applications commonly run off a flat datasheet. This has numerous advantages, such as allowing for intuitive filtering on hierarchical data, working with the entire database without having a huge number of columns, and requiring no data manipulation at all. The disadvantage is the tool can only analyse database exports in the EBMT registry format, and can only run the predefined analyses, while most statistical applications are not limited to specific formats and specific analyses.

To aid centres that participate in EBMT benchmarking, we incorporated a filter that selects transplants eligible to be included in benchmarking in the tool [16]. This can be used in advance of benchmarking, to ensure adequate and complete data is used for it, and review outcome in anticipation of benchmarking results, or after benchmarking, to perform subgroup analyses and track down where deviations from expected survival occur.

It is important to note the nature of the tool is primarily scientific, to prove a useful tool can be created based on the standardized export a patient registry offers. We have proven such a tool can be created, that it can run fully offline to ensure privacy and security, and that it can be extensible, to allow centres to add to and adjust the tool to fit their needs. As such, this work may be relevant to other patient registries, as large registries exist for many diseases, and quality of care is globally important.

The basic framework of the tool, including the use of Shiny and electron, the modular build-up with more complex modules for data ingest, filtering and grouping, and easy-to-build modules that take the filtered, grouped data and run analyses, while being able to export the data as analysed, can be used as a template to build secure, extensible outcome analysis tools for all diseases and registries.

The current EBMT registry does not offer data using a standardized metadata format. However, the new EBMT registry will use the Observational medical outcomes partnership - Common Data Model (OMOP-CDM), using standardized metadata tailored for retrospective observational analyses [17]. R connectors and other R tools for OMOP-CDM databases exist, which means that work retrieving data and interpreting metadata could be shifted from the outcome analysis tool to a specialized tool, reducing complexity. This could provide exciting new possibilities in the future, both for extending this tool and similar ones, as well as integrating existing tools, and collaborating with other users of OMOP-CDM.

We have described the development of a dedicated, clinically-useful software and its initial validation in the setting of HSCT datasets which serves as a model for evaluation of centre outcomes on a local level, along broader national and international data-based systems. We fully recognise that such applications are subject to ongoing version updates, especially in clinical settings, so that utility remains current and relevant. We hope to maintain applicability and validity in the future by version updates, although these will be subject to uptake across the HSCT community and resource considerations.

More generally, we conclude that, as standardization and data registration continue to increase and are able to support quality improvement systems within healthcare, future software tools building on this foundation will facilitate centres routinely entering data into registries to conduct detailed local appraisal to gain insights into patient outcomes and influencing factors, not only within the field of HSCT and but also in other specialities, while being able to customize such tools to their needs and ensuring privacy and security by working offline.

DATA AVAILABILITY

The most recent version of the tool is available on Zenodo on https://doi.org/10.5281/zenodo.7318445, both as source code and as an installer, under the open GPLv3 license. The version of the tool as of the writing of this manuscript, version 0.1.0, is available on Zenodo under https://doi.org/10.5281/zenodo.7318446.

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AUTHOR CONTRIBUTIONS

EvA designed the study, developed the tool, performed analyses and drafted the manuscript. HP gave input on filters and analyses and reviewed the manuscript. AM, MS, and JS reviewed the manuscript. RS gave input on the tool, tested it at his center, and reviewed the manuscript. AL designed the study, gave input on the tool, and reviewed the manuscript.

COMPETING INTERESTS

All authors declared no competing interests.

ADDITIONAL INFORMATION

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