IQWiG Reports – Commission No. V21-04

Relationship between volume of services and quality of treatment outcome for stem cell transplantations – Update on commission V18-02[1]

Extract

[1] Translation of Chapters 1 to 7 of the rapid report V21-04 *Zusammenhang zwischen Leistungsmenge und Qualität des Behandlungsergebnisses bei Stammzelltransplantationen – Aktualisierung zum Auftrag V18-02* (Version 1.0; Status: 2 August 2021 [German original], 20 January 2022 [English translation]). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Relationship between volume of services and quality of treatment outcome for stem cell transplantations – Update on commission V18-02

Commissioning agency:
Federal Joint Committee

Commission awarded on:
15 April 2021

Internal Commission No.:
V21-04

Address of publisher:
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This report on the update of rapid report V18-02 was prepared without collaboration of external experts.

The responsibility for the contents of the report lies solely with IQWiG.

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Keywords: Minimum Volume, Stem Cell Transplantation, Systematic Review

Key statement

Research question

The objective of this investigation is to update Rapid Report V18-02. Hence, this rapid report aims to answer the same research questions as Rapid Report V18-02:

present and assess the correlation between volume and quality of treatment outcome in allogeneic stem cell transplantation (SCT) in adults (research question 1a)

present and assess the correlation between volume and quality of treatment outcome in autologous SCT in adults (research question 1b)

present and assess studies which investigate the effects of a minimum number of cases of SCT introduced into the healthcare system on the quality of treatment outcomes (research question 2)

Conclusion

For the investigation of any correlation between volume and quality of treatment outcome in allogeneic SCT (research question 1a) and autologous SCT (research question 1b), the present rapid report was able to include 1 observational study each. Both studies investigated volume solely on the transplantation centre (TC) level and quality of treatment outcome solely for the outcome of all-cause mortality.

Regarding allogeneic SCT, on the basis of 1 study of high informative value of results, the present rapid report derived a correlation between volume and quality of treatment outcome in favour of higher-volume TCs for the outcome of all-cause mortality. This result supports the conclusion of Rapid Report V18-02.

Regarding autologous SCT, the 1 study of low informative value of results did not allow the present rapid report to derive any correlation between TC volume and quality of treatment outcome. This result does not alter the conclusion of Rapid Report V18-02, which derived a correlation.

No studies were found for investigating the effects of specific minimum case numbers implemented in patient care for SCT on the quality of treatment outcomes (research question 2).

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List of abbreviations

Abbreviation	Meaning
CI	confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
DRST	Deutsches Register für Stammzelltransplantationen (German Registry for Stem Cell Transplantation)
EBMT	European Society for Blood and Marrow Transplantation
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
OR	odds ratio
SCT	stem cell transplantation
TC	transplantation centre

1 Background

This document is an update of Rapid Report V18-02 [1], which discussed the relationship between the volume of services (hereinafter "volume") and the quality of treatment outcome in stem cell transplantation.

Background information on the commissioning of the update is found in Chapter 3 of this document. Please refer to Rapid Report V18-02 for background information on the subject of the commission.

2 Research question

The objective of this investigation is to update Rapid Report V18-02. Hence, this rapid report aims to answer the same research questions as Rapid Report V18-02:

- present and assess the correlation between volume and quality of treatment outcome in allogeneic stem cell transplantation in adults (research question 1a)
- present and assess the correlation between volume and quality of treatment outcome in autologous stem cell transplantation in adults (research question 1b)
- present and assess studies which investigate the effects of a minimum number of cases of stem cell transplantation introduced into the healthcare system on the quality of treatment outcomes (research question 2)

3 Course of the project

On 16 August 2018, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) with a systematic literature search and evaluation of the evidence on the correlation between volume and quality of treatment outcome in stem cell transplantation. IQWiG researched and assessed the current knowledge about the relationship between volume and quality of treatment outcome in stem cell transplantation and presented the results to the G-BA in the form of Rapid Report V18-02 [1] in June 2019. With its letter dated 15 April 2021, the G-BA commissioned IQWiG with a systematic literature search and evidence assessment to update Rapid Report V18-02.

The present rapid report was written on the basis of the research questions and methods of Rapid Report V18-02, sent to G-BA, and published 4 weeks later on the IQWiG website.

4 Methods

As a supplement of Rapid Report V18-02 [1], this rapid report includes a search update and an evidence assessment of studies published after the previous systematic search (8 December 2018). The criteria for study inclusion as well as the methods for information procurement and assessment have already been discussed in Rapid Report V18-02 and were applied in the present rapid report as well.

5 Results

5.1 Comprehensive information retrieval

5.1.1 Primary information sources

Figure 1 presents the results of the current systematic literature search in the bibliographic databases and the study selection according to the criteria for study inclusion. The search strategies for the search in bibliographic databases are found in Appendix A. The most recent search was conducted on 19 April 2021 and took into account studies published after the date of the previous systematic search (8 December 2018).

The references of the hits screened at full-text level but excluded are found in Section 9.1 of the full report, with the respective reason for exclusion.

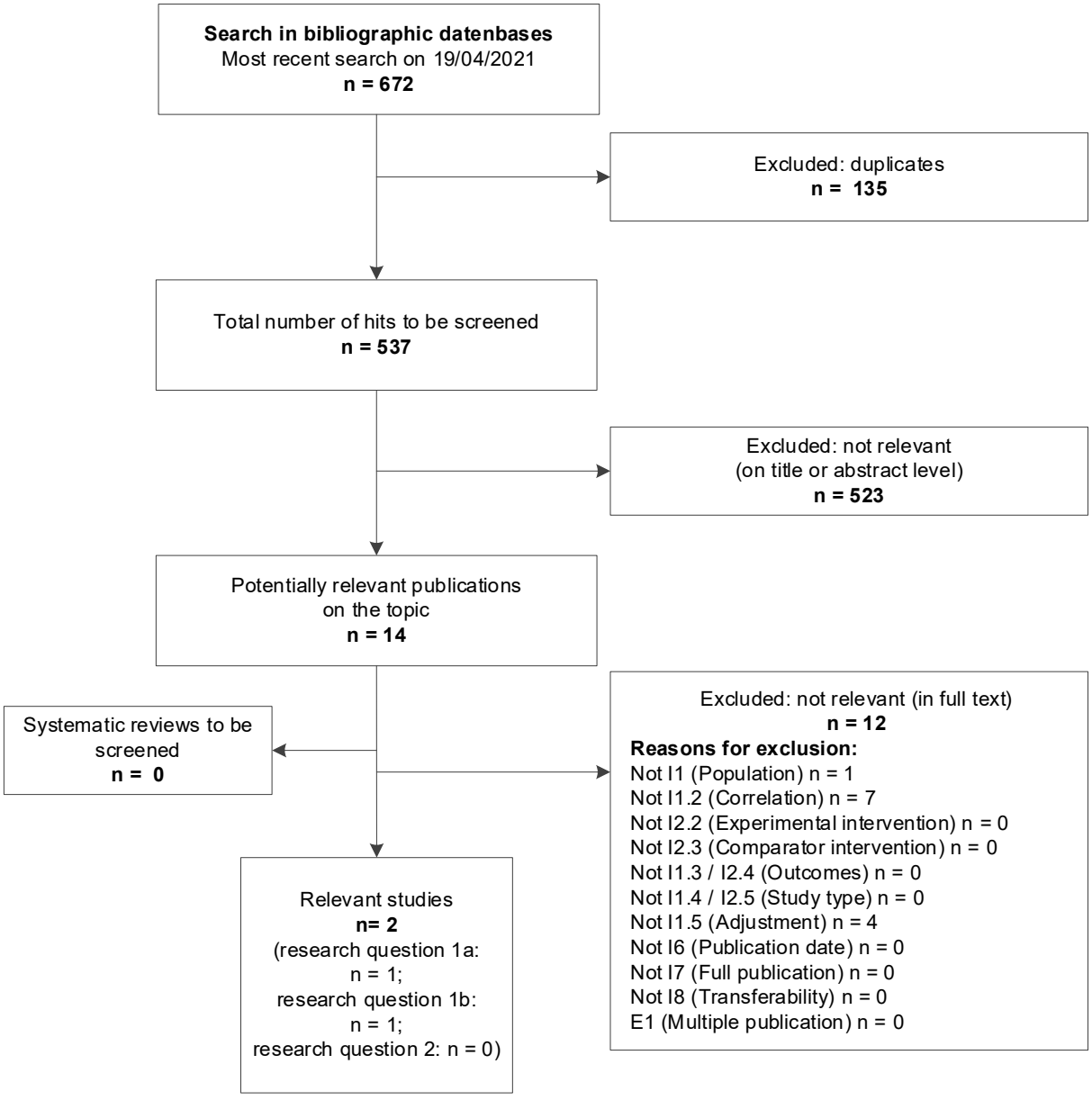

Figure 1: Result of the update of the bibliographic search and study selection

5.1.2 Further information sources and search techniques

Relevant studies or documents found through further information sources and search techniques are presented below unless they were already found through primary information sources.

5.1.2.1 Use of further search techniques

The information retrieval did not find any relevant systematic reviews.

5.1.2.2 Requests to authors

No requests to authors to obtain additional information on relevant studies were necessary since such information was not expected to have a relevant impact on the assessment.

5.2 Resulting study pool

Through the various search steps, a total of 2 current relevant studies (2 documents) were found (also see Table 1). One study was found for answering research question 1a and 1 study for research question 1b.

No reliable studies were found to answer research question 2.

Table 1: Study pool for research questions 1a and 1b

Study	Full publication (in professional journals)	Relevant for
Jansen 2020	Yes [2]	Research question 1b
Majhail 2020	Yes [3]	Research question 1a

5.3 Characteristics of the studies included in the assessment

The characteristics of the studies included to answer research questions 1a and 1b are presented in Table 2 and summarized below.

Table 2: Characteristics of the included studies

Study / study design[a] (data source)	Recruitment country / follow-up period[b] / study objective	Inclusion and exclusion criteria	Transplantation procedure	Total number of units	Volume definition / number of TCs per volume category
Jansen 2020 / retrospective observational study (data from DRST and the RKI Centre for Cancer Registry Data)	Germany / 2001–2014[c] / Investigation of any correlation between TC volume and overall survival and the utilization patterns of autologous SCT in first-line therapy	Inclusion criteria: ▪ First autologous SCT ▪ Patients with multiple myeloma [ICD-10: C90.0] Exclusion criteria: ▪ Period between diagnosis and transplantation > 12 months ▪ TCs in which > 15% patients lack documented follow-up ▪ Patients without documented follow-up	Autologous SCT in first-line therapy	8564[d] patients. 77 TCs	Total annual autologous SCTs per TC (mean of the 3 years prior to the year of transplantation) / TCs categorized in quintiles by volume: ▪ Quintile 1: 0.0–8.2 ▪ Quintile 2: 8.3–13.9 ▪ Quintile 3: 14.0–20.9 ▪ Quintile 4: 21.0–30.9 ▪ Quintile 5: 31.0–102.7
Majhail 2020 / retrospective observational study (data from CIBMTR and a TC survey)	USA / 2008–2010[e] / Investigation of any correlation between TC volume, infrastructure, staff structure, and care models on the one hand and overall survival on the other	Inclusion criteria: ▪ First allogeneic SCT ▪ Patients who died within the first 12 months or had a follow-up period ≥ 11 months Exclusion criteria: ▪ TCs which did not participate in the survey ▪ TCs with incomplete documentation of patient data in the CIBMTR	Allogeneic SCT	11 537 patients 83 TCs	Total number of allogeneic SCTs in 2010 / volume category per TC: ▪ Low volume: ≤ 40, 42 TCs ▪ High volume: > 40, 41 TCs

a: If a study, e.g. secondary data analysis or registry study, specified a data source, it is entered here.
b: In secondary data analyses or registry studies, for instance, the follow-up duration is the data collection period.
c: Registry data from 1998 to 2000 were used additionally to calculate the mean volume per TC.
d: Discrepant data in the publication (text, table, flow chart [Supplementary Figure 1]).
e: The TC survey for determining TC characteristics was conducted in 2012.

CIBMTR: Center for International Blood and Marrow Transplant Research; DRST: German Registry for Stem Cell Transplantation; ICD: International Classification of Diseases and Related Health Problems; RKI: Robert Koch Institute; SCT: stem cell transplantation; TC: transplantation centre

5.3.1 Study design and data source

The 2 included studies are retrospective observational studies.

The Jansen 2020 study is based on data from the German Registry for Stem Cell Transplantation (DRST) and the Centre for Cancer Registry Data of the Robert Koch Institute (RKI) [2].

The authors of the Majhail 2020 study used data from the Center for International Blood and Marrow Transplant Research (CIBMTR) and a TC survey [3].

5.3.2 Recruitment countries, follow-up period, and study objective

The Jansen 2020 study [2] was conducted in Germany, while the Majhail 2020 study [3] was carried out in the United States.

The Jansen 2020 study included patients who received their first autologous stem cell transplantation (SCT) in the period 2001 through 2014. The Majhail 2020 study is based on data from patients who had undergone their first allogeneic SCT between 2008 and 2010.

In both studies, a primary objective was the investigation of any correlation between TC volume and overall survival.

5.3.3 Main inclusion criteria of the studies and transplantation method

Jansen 2020 included patients with multiple myeloma who underwent their first autologous SCT within the first 12 months after diagnosis. The study excluded patients without documented follow-up as well as transplantation centres (TCs) in which more than 15% of patients lacked documented follow-up [2].

Majhail 2020 included patients who received their first allogeneic SCT. It excluded TCs which did not participate in the TC characteristics survey as well as TCs which failed to fully document patient data in the CIBMTR [3].

5.3.4 Volume definition

The included studies defined volume as the total number of autologous or allogeneic SCTs performed annually in each TC. Jansen 2020 [2] used the average number of autologous SCTs performed in the 3 years prior to the performed SCT. Majhail 2020 [3] used the number of allogeneic SCTs conducted in 2010 as the TC volume.

In Jansen 2020, volume was analysed both continuously and categorically. For the categorical analysis, TCs were grouped into quintiles by volume. Majhail 2020 conducted a categorical analysis only, using a dichotomous categorization; the threshold of 40 allogeneic SCTs annually as determined through maximum likelihood estimation was close to the median.

None of the studies investigated the relationship between volume and quality of treatment outcome at the level of the physician or the TC-physician combination.

5.3.5 Data on the study population

The main characteristics of the study populations used to answer research questions 1a and 1b are presented in Appendix B of the full report and summarized below.

Jansen 2020 [2] provided slightly discrepant information on the number of included patients. We suspect that 8564 patients were included. Majhail 2020 [3] included 11 537 patients. Both studies provided the patient age structure, while the sex ratio is presented only in Jansen 2020.

Table 3 provides an overview of the primary diseases of the patients treated with allogeneic or autologous SCT in each study.

Table 3: Overview of the primary diseases reviewed in the studies

Transplantation type **Study**	**Primary haematological disease**							
	Acute leukaemia	**Chronic leukaemia**	**Malignant lymphoma**	**Plasma cell disease**	**Myelodysplastic syndrome / myeloproliferative neoplasm**	**Other malignant disease**	**Severe aplastic anaemia**	**Other nonmalignant disease**
Allogeneic SCT								
Majhail 2020	●	●	●	●	●	●	●	●
Autologous SCT								
Jansen 2020	-	-	-	●[a]	-	-	-	-

●: Data on this primary disease were reported.
-: No data were reported.
a: Exclusively multiple myeloma.
SCT: stem cell transplantation

To allow a breakdown by primary disease severity, Jansen 2020 [2] provided the patients' stage distribution as per the Durie-Salmon staging system for multiple myeloma. Majhail 2020 [3] provided information about the patients' primary diseases, with acute myeloid leukaemia being the most common disease at about 37.6%. For the description of general health status, both studies provided the Karnofsky index, with Majhail 2020 additionally reporting the Haematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI) score.

5.4 Assessment of the informative value of results (research questions 1a and 1b)

Table 4 presents the informative value of results.

The most important criteria for rating the informative value of results were high data quality, adequate patient flow, appropriate consideration of cluster effects, sufficient risk adjustment, adequate handling of missing data, and adequate reporting of relevant aspects.

The informative value of results is rated as high for Majhail 2020 [3] and as low for Jansen 2020 [2].

The included studies used data from clinical registries, but only Majhail 2020 provided high-quality data. In Jansen 2020, the percentage of missing values in patient characteristics was too high for this problem to be fully resolved by the employed statistical method of multiple imputation. Therefore, the quality of individual data from Jansen 2020 was rated as unclear. In addition, the text, tables, and patient flow chart of Jansen 2020 provided discrepant information as to the number of included patients, without offering an explanation for these differences. Therefore, patient flow was rated as unclear for Jansen 2020. The patient flow in Majhail 2020 was rated as adequate because in addition to clearly listing inclusion and exclusion criteria, the study provided information on drop-outs.

The included studies took into account cluster effects and described the statistical methods used for doing so.

In both studies, adequate risk adjustment was conducted on the level of the patient, the transplantation method, and the TC. Jansen 2020 investigated interaction effects between TC characteristics and the other factors. Since these tests failed to reveal any significant relationships, the study's final model did not include any other factors on the TC level. Table 5 and Table 6 show an overview of the relevant risk factors the studies took into account on the patient level or on the level of the transplantation method and the TC.

Jansen 2020 limited the analysis period in some cases, without providing any reasons for doing so. Therefore, the reporting in the Jansen 2020 study was deemed inadequate. The statistics part of the Majhail 2020 publication and the legend of the results table provided discrepant information on the risk factors included in the final model. Since the inconsistently mentioned risk factor of "year transplantation performed" was not absolutely necessary for an adequate risk adjustment, this deficiency did not unfavourably affect the study's rating.

Jansen 2020 analysed the relationship between volume and quality of treatment outcome both continuously and categorically. Categorical analysis can entail a loss of information. In addition, the linearity assumption may be violated within the individual categories. Further, categorical analysis may provide less reliable results than continuous analysis [4]. Therefore, the present rapid report included the results only of continuous modelling. Majhail 2020 conducted exclusively a categorical analysis.

The included studies did not provide any information on a check of model quality, but they did validate the statistical model. Effect estimates, including data on precision, were provided in the studies.

Given that data is readily available, adequate presentation of data flow, appropriate consideration of cluster effects, adequate handling of missing data, sufficient risk adjustment, and complete reporting of results, the informative value of results of Majhail 2020 was rated as high. The key factors for the low rating of the informative value of the Jansen 2020 results were unclear data quality, discrepant information on patient flow, and inadequate reporting of relevant aspects.

Table 4: Informative value of results

Study	High quality of individual data[a]	Adequate patient flow	Volume analysis	Plausible procedure for determining the volume thresholds	Suitable model class	Adequate procedure for considering cluster effects	Adequate risk adjustment on all levels[a]	Adequate handling of missing data	Information on a check of model quality	Model validation	Information on point estimate, including precision	Adequate reporting of relevant aspects	Further aspects	Informative value of results
Jansen 2020	Unclear	Unclear	Continuous[b]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	▪ Voluntary participation in DRST	Low
Majhail 2020	Yes	Yes	Categorical	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes[c]	▪ Legal obligation to report all allogeneic SCTs ▪ Voluntary participation in the TC survey	High

a: "Yes" or "no" was stated only if unambiguous information was available for the specific study.
b: The study additionally presents a categorical analysis, but these results were not used for this rapid report.
c: Discrepant information provided in the publication on the risk factors included in the final model.

DRST: German Registry for Stem Cell Transplantation; SCT: stem cell transplantation; TC: transplantation centre

Table 5: Patient-level risk factors taken into account in the adjustment

Study	Risk factors																	
	Patient																	
	Primary disease	Durie-Salmon stage and subclassification	Type of multiple myeloma	Light chain type (kappa, lambda, others)	Immunoglobulin type (A, G, others)	Age	Sex	Ancestry	Disease status	Duration of illness	EBMT risk score	Karnofsky Performance Score at transplantation	HCT-CI score	Remission status	Prior autologous stem cell transplantation	Sensitivity to chemotherapy (autologous)	Cytogenetic abnormalities	Cytomegalovirus status
Jansen 2020	x	●	●	●	●	●	●	-	-	-	-	●	-	-	-	-	-	-
Majhail 2020	●[a]	-	-	-	-	●	-	●	●	-	-	●	●	-	●	●[b]	-	●

●: Risk factor taken into account in the adjustment.
x: Risk factor irrelevant for study since the study refers to only 1 primary disease.
-: No adjustment made for this risk factor.
a: It is unclear whether this risk factor was included in the final model. Discrepant data provided in the statistics part of the publication and the legend of the results table.
b: Only for non-Hodgkin lymphoma and Hodgkin lymphoma.
EBMT: European Society for Blood and Marrow Transplantation; HCT-CI: Hematopoietic Cell Transplantation-Specific Comorbidity Index

Table 6: Risk factors on the transplantation method and TC level taken into account in the adjustment

Study	Risk factors											
	Transplantation method							TC				
	Year transplantation performed	Conditioning	GvHD prophylaxis (allogeneic)	Stem cells from peripheral blood or bone marrow	Donor-recipient sex match	Donor type HLA match	Donor age	Accreditation	Time from diagnosis to transplantation	Affiliation with medical school	Initial contact in emergencies / outside surgery hours	Gross national income per capita
Jansen 2020	●	-	x	-	x	x	x	-	-[a]	-	-	-
Majhail 2020	●[b]	●[c]	-	●	●	●	●[d]	-	●[e]	-	-	-

●: Risk factor taken into account in the adjustment.
x: Risk factor irrelevant for study since the study investigates only autologous SCT.
-: No adjustment made for this risk factor.
a: Adjustment by this risk factor was conducted only in the sensitivity analyses.
b: Unclear whether this risk factor was included in the final model for all outcomes. Discrepant data provided in the statistics part of the publication and the results table legend.
c: In leukaemia.
d: In unrelated recipients.
e: In acute myeloid leukaemia and acute lymphatic leukaemia.

GvHD: graft versus host disease; HLA: human leukocyte antigen; SCT: stem cell transplantation; TC: transplantation centre

5.5 Overview of outcomes relevant for the assessment

The 2 included studies were suitable for extracting data on only 1 relevant outcome, all-cause mortality. Table 7 provides an overview of all assessment-relevant outcomes for which data were extracted to answer research questions 1a and 1b.

The included studies provided no data on the outcomes of treatment-related mortality, non-relapse mortality, disease-free survival, adverse effects of therapy, and health-related quality of life, including activities of daily living and dependence on help from others.

Table 7: Matrix of relevant outcomes

Study	Outcomes					
	Mortality			Morbidity		QoL
	All-cause mortality	Treatment-related mortality	Non-relapse mortality	Disease-free survival	Adverse effects of therapy	Health-related quality of life
Allogeneic SCT						
Majhail 2020	●	-	-	-	-	-
Autologous SCT						
Jansen 2020	●	-	-	-	-	-

●: Data were reported and were usable.
-: No data were reported.
QoL: health-related quality of life; SCT: stem cell transplantation

5.6 Results on relevant outcomes

The studies included in the present rapid report provided results only for the assessment-relevant outcome of all-cause mortality [2,3]. Below, the results on this outcome are presented separately for allogeneic SCT (research question 1a) and autologous SCT (research question 1b).

The included studies did not identify any results for physician volume or TC-physician volume.

5.6.1 Results on the outcome of all-cause mortality

Allogeneic SCT

One study of high informative value of results reported results for the outcome of all-cause mortality at the time point 100 days or 1 year after allogeneic SCT (see Table 8).

In Majhail 2020 [3], a statistically significant difference in favour of the higher-volume TCs was found for all-cause mortality both after 100 days and after 1 year (100 days: odds ratio [OR]: 1.41; 95% confidence interval [CI]: [1.16; 1.72]; p-value: < 0.001; 1 year: OR: 1.32; 95% CI: [1.13; 1.55]; p-value: < 0.001).

Autologous SCT

One study reported results on the outcome of all-cause mortality following autologous SCT (see Table 9).

In Jansen 2020 [2], rated as having a low informative value of results, no statistically significant difference in all-cause mortality following autologous SCT in first-line therapy was found for multiple myeloma patients after 1 year.

Summary

Overall, for allogeneic SCT, 1 study of high informative value of results showed a correlation between TC volume and quality of treatment outcome in favour of higher-volume TCs for all-cause mortality. For autologous SCT, on the basis of 1 study of low informative value of results, it was not possible to derive any correlation in multiple myeloma patients. The relationship between physician volume or combined TC-physician volume and this outcome was not investigated.

Table 8: Results – all-cause mortality following allogeneic stem cell transplantation

Study / underlying diseases	Outcome definition	N	Volume specification	Raw overall survival; n (%)	Adjusted odds ratio [95% CI]; p-value
Majhail 2020	Overall survival	11 537	TC volume in the year 2010		
▪ Acute leukaemia	After 100 days				
▪ Chronic leukaemia		1900	≤ 40	1577[a] (83)	Reference category
▪ Malignant lymphoma		9637	> 40	8288[a] (86)	1.41 [1.16; 1.72][c]; < 0.001[d]
▪ Plasma cell disease				p < 0.001[b]	
▪ Myelodysplastic syndrome / myeloproliferative neoplasm	After 1 year				
▪ Other malignant disease		1900	≤ 40	1064[a] (56)	Reference category
▪ Severe aplastic anaemia		9637	> 40	5975[a] (62)	1.32 [1.13; 1.55][c]; < 0.001[d]
▪ Other nonmalignant disease				p < 0.001[b]	

a: IQWiG calculations.
b: Log rank test.
c: Values > 1 indicate an advantage for high-volume TCs.
d: p-value from a multivariate logistic regression model.

CI: confidence interval; N: number of analysed patients; n: number of patients with an event; TC: transplantation centre

Table 9: Results – all-cause mortality following autologous stem cell transplantation

Study / underlying diseases	Outcome definition	N	Volume specification	Raw overall survival; n (%)	Adjusted odds ratio [95% CI]; p-value
Jansen 2020 ▪ Multiple myeloma	Overall survival after 1 year	8564[a]	Per increase by 3 transplantations per TC and year	2819 (33)	1.00 [0.98; 1.01]; 0.4776[b]

a: Discrepant information provided in the publication (text, table, flowchart [Supplementary Figure 1]).
b: Test unclear.

CI: confidence interval; N: number of analysed patients; n: number of patients with an event; TC: transplantation centre

5.6.2 Results on treatment-associated mortality

None of the included studies reported data on the outcome of treatment-related mortality.

5.6.3 Reports on non-relapse mortality

None of the included studies reported data on the outcome of non-relapse mortality.

5.6.4 Results on disease-free survival

None of the included studies reported data on the outcome of disease-free survival.

5.6.5 Results on adverse effects of therapy

None of the included studies reported data on the outcome of adverse effects of therapy.

5.6.6 Results on the outcome of health-related quality of life, including activities of daily living and dependence on help from others

None of the included studies provided data on the outcome of health-related quality of life, including activities of daily living and dependence on help from others.

5.6.7 Metaanalyses

For the reported outcome of all-cause mortality, it was impossible to prepare a metaanalytical summary of results because the 2 included studies investigated different transplantation procedures, allogeneic SCT versus autologous SCT.

5.6.8 Subgroup attributes

Jansen 2020 [2] (low informative value of results) conducted subgroup analyses of multiple myeloma patients for different age groups and periods during which SCT was performed (see Table 10).

The conclusions to be drawn from the results of the subgroup analyses do not differ from those of the results on the outcome of all-cause mortality following autologous SCT (see Section 5.6.1).

Table 10: Results – subgroup analyses of all-cause mortality following autologous stem cell transplantation

Study / primary diseases	Outcome definition	N	Volume specification	Raw overall survival; n (%)	Adjusted odds ratio [95% CI]; p-value
Jansen 2020	**Age [years]**				
▪ Multiple myeloma	Overall survival	8564[a]	Per increase by 3 transplantations per TC and year		
	< 65 years	6358[b]		ND	1.00 [0.99; 1.01]; 0.5124[c]
	≥ 65 years	2206[b]		ND	0.99 [0.97; 1.01]; 0.3356[c]
	Year transplantation performed				
	Overall survival	ND	Per increase by 3 transplantations per TC and year		
	2001–2004			ND	0.99 [0.98; 1.25]; 0.6035[c]
	2005–2008			ND	0.99 [0.98; 1.01]; 0.3317[c]
	2009–2012[d]			ND	1.00 [0.98; 1.01]; 0.8616[c]

a: Discrepant information provided in the publication (text, table, flowchart [Supplementary Figure 1]).
b: IQWiG calculations.
c: Test unclear.
d: The years 2013 and 2014 are missing. According to the analyses conducted in the study (Figure 1A), the number of autologous SCTs increased substantially in the years 1999 through 2013.

CI: confidence interval; N: number of analysed patients; n: number of patients with an event; ND: no data; SCT: stem cell transplantation; TC: transplantation centre

5.7 Overall evaluation of results

The results of the present rapid report do not change the conclusion drawn in Rapid Report V18-02 regarding the relationship between volume and quality of treatment outcome following allogeneic or autologous SCT.

In the present rapid report, 1 study was found for allogeneic SCT and 1 study for autologous SCT; they both investigated the relationship between volume and quality of treatment outcome (research questions 1a and 1b), 1 of them being of high informative value of results. Data were available only on the outcome of all-cause mortality and only for volume defined on the TC level. None of the included studies investigated the relationship between volume and quality of treatment outcome on the physician level or for the combination of TC-physician volume.

For the outcome of all-cause mortality, on the basis of 1 study of high informative value of results, a correlation between volume and quality of treatment outcome was derived for allogeneic SCT; the correlation was in favour of higher TC volume. This confirms the correlation derived in Rapid Report V18-02 for allogeneic SCT on the TC level. For autologous SCT, it was not possible to derive any correlation between TC volume and quality of treatment outcome on the basis of 1 study of low informative value of results. This study does not call into question the correlation derived in Rapid Report V18-02 for autologous SCT; this is because the studies cited in Rapid Report V18-02 on this research question (Gratwohl 2015 and Gratwohl 2014) were not restricted to a single primary disease, but rather took into account a wide range of primary diseases. After all, the research question of the rapid report is not restricted to a specific primary disease, but generally covers underlying haematopoietic diseases which can be treated with autologous SCT.

The included studies provided no data for either allogeneic SCT or autologous SCT regarding the outcomes of treatment-related mortality, non-relapse mortality, disease-free survival, adverse effects of therapy, and health-related quality of life, including activities of daily living and dependence on help from others. Hence, the present update did not produce any new data on the relationship between volume and quality of treatment outcome for these outcomes, and with regard to these outcomes, there is no change to the results of Rapid Report V18-02.

Given that no studies of high informative value were found, neither Rapid Report V18-02 nor this update allow drawing any conclusions on the effects of a minimum number of cases of introduced into the healthcare system for stem cell transplantation on the quality of treatment outcome (research question 2).

Taking into account both Rapid Report V18-02 and the present rapid report, Table 11 summarizes the included studies' results regarding the relevant outcomes for allogeneic SCT (research question 1a), and Table 12 does the same for autologous SCT (research question 1b).

Table 11: Overview of the outcome results and volume-outcome relationship in allogeneic SCT as observed in Rapid Report V18-02 and the present rapid report (multipage table)

	Instruments											
	All-cause mortality	**EFS**	**Treatment-related mortality**	**Non-relapse mortality**	**Disease-free survival**		**Serious, life-threatening, or fatal aGvHD or cGvHD**	**Serious, life-threatening, or fatal infections**	**Occurrence of secondary neoplasms**	**Further serious treatment-related complications**	**Serious adverse events**	**Health-related quality of life**
					RFS	**RI**						
TC level												
Results of outcomes following allogeneic SCT when comparing high versus low volume	↑[a]	(↑)[b]	-	(↑)	(↑)	(↔)	-	-	-	-	-	-
Physician level:												
Results of outcomes following allogeneic SCT when comparing high versus low volume	↑	-	-	-	-	-	-	-	-	-	-	-
Level of TC-physician volume combination												
Results of outcomes following allogeneic SCT when comparing high versus low volume	-	-	-	-	-	-	-	-	-	-	-	-

Table 11: Overview of the outcome results and volume-outcome relationship in allogeneic SCT as observed in Rapid Report V18-02 and the present rapid report (multipage table)

	Instruments											
	All-cause mortality	**EFS**	**Treatment-related mortality**	**Non-relapse mortality**	**Disease-free survival**		**Serious, life-threatening, or fatal aGvHD or cGvHD**	**Serious, life-threatening, or fatal infections**	**Occurrence of secondary neoplasms**	**Further serious treatment-related complications**	**Serious adverse events**	**Health-related quality of life**
					RFS	**RI**						
Correlation between volume and quality of treatment outcome	Correlation in favour of high volume on the TC and physician level.	Correlation in favour of high TC volume	No conclusion can be drawn.	Correlation in favour of high TC volume	Correlation in favour of high TC volume	No correlation found.	No conclusion can be drawn.	No conclusion can be drawn.	No conclusion can be drawn.	No conclusion can be drawn.	No conclusion can be drawn.	No conclusion can be drawn.

↑: Based on 1 study of high informative value of results showing statistically significant differences in outcome in favour of higher-volume TCs and/or physicians. Studies of low informative value of results do not call this association into question.
(↑): Largely based on 1 or more studies of low informative value of results showing statistically significant differences in outcome in favour of higher-volume TCs and/or physicians. Studies with results which are not statistically significant point in the same direction or do not call the association into question.
(↔): Studies of low informative value of results showed no statistically significant differences in favour of high-volume TCs.
-: The included studies did not report any (usable) data.
a: Rapid Report V18-02 was based exclusively on results from several studies of low informative value of results.
b: Correlation applies only to the disease-specific definition of volume.

aGvHD: acute graft-versus-host disease; cGvHD: chronic graft-versus-host disease; EFS: event-free survival; RFS: relapse-free survival; RI: relapse incidence; SCT: stem cell transplantation; TC: transplantation centre

Table 12: Overview of the outcome results and volume-outcome relationship in autologous SCT as observed in Rapid Report V18-02 and the present rapid report (multipage table)

	Instruments										
	All-cause mortality	**EFS**	**Treatment-related mortality**	**Non-relapse mortality**	**Disease-free survival**		**Serious, life-threatening, or fatal infections**	**Occurrence of secondary neoplasms**	**Further serious treatment-related complications**	**Serious adverse events**	**Health-related quality of life**
					RFS	**RI**					
TC level											
Results of outcomes following autologous SCT when comparing high versus low volume	(↑)	-	-	(↔)	(↑)	(↑)	-	-	-	-	-
Physician level:											
Results of outcomes following autologous SCT when comparing high versus low volume	↑	-	-	-	-	-	-	-	-	-	-
Level of TC-physician volume combination											
Results of outcomes following autologous SCT when comparing high versus low volume	-	-	-	-	-	-	-	-	-	-	-

Table 12: Overview of the outcome results and volume-outcome relationship in autologous SCT as observed in Rapid Report V18-02 and the present rapid report (multipage table)

	Instruments										
	All-cause mortality	**EFS**	**Treatment-related mortality**	**Non-relapse mortality**	**Disease-free survival**		**Serious, life-threatening, or fatal infections**	**Occurrence of secondary neoplasms**	**Further serious treatment-related complications**	**Serious adverse events**	**Health-related quality of life**
					RFS	**RI**					
Relationship between volume and quality of treatment outcome	Correlation in favour of high volume on the TC and physician level.	No conclusion can be drawn.	No conclusion can be drawn.	No correlation found.	Correlation in favour of high TC volume	Correlation in favour of high TC volume	No conclusion can be drawn.	No conclusion can be drawn.	No conclusion can be drawn.	No conclusion can be drawn.	No conclusion can be drawn.

↑: Based on 1 study of high informative value of results showing statistically significant differences in the outcome in favour of higher-volume physicians.
(↑): Largely based on 1 or more studies of low informative value of results showing statistically significant differences in outcome in favour of higher-volume TCs and/or physicians. Studies with results which are not statistically significant point in the same direction or do not call the association into question.
(↔): Studies of low informative value of results showed no statistically significant differences in favour of high-volume TCs.
-: The included studies did not report any (usable) data.

EFS: event-free survival; RFS: relapse-free survival; RI: relapse incidence; SCT: stem cell transplantation; TC: transplantation centre

6 Discussion

Classification of the assessment results

The present rapid report is an update of Rapid Report V18-02 [1] and hence supplements the latter's results on the potential correlation between volume and quality of treatment outcome in allogeneic and autologous SCT.

Rapid Report V18-02 and the present rapid report as its update each included 1 study of high informative value of results. In the present rapid report, this was Majhail 2020 [3], which investigated the relationship between TC volume and quality of treatment outcome for allogeneic SCT. Loberiza 2005 [5], the study with a high informative value of results which was included in Rapid Report V18-02, looked instead at physician volume. Both studies investigated only the outcome of all-cause mortality; for allogeneic SCT, they demonstrate a correlation between volume and quality of treatment outcome in favour of higher-volume TCs or higher-volume physicians. Like Majhail 2020, the results of Gratwohl 2015 [6] and Gratwohl 2014 [7], which were included in Rapid Report V18-02 and had a low informative value of results, showed a decrease in all-cause mortality as TC volume increased.

The only German study qualifying for inclusion in Rapid Report V18-02 or the present rapid report is Jansen 2020 [2]. At a low informative value of results, this study investigated the relationship between TC volume and quality of treatment outcome for autologous SCT. For patients with multiple myeloma, it was not possible to derive any correlation from this study. However, its non-significant result does not call into question the correlation in favour of higher-volume TCs which was derived in Rapid Report V18-02. After all, Gratwohl 2015 and Gratwohl 2014, which were included in Rapid Report V18-02, reported a statistically significantly lower all-cause mortality for TCs with higher annual volume based on patients with a wider range of primary diseases. The authors of Jansen 2020 explain the difference between their results and those of comparable studies by the fact that they included only patients with a first autologous SCT. Gratwohl 2015 and Gratwohl 2014, however, likewise included only patients with a first autologous SCT. The primary diseases included in the investigation might explain why results found by Jansen 2020 differ from those found by Gratwohl 2015 and Gratwohl 2014. Jansen 2020 included only patients with multiple myeloma, while Gratwohl 2014 and Gratwohl 2015 included patients with a wide range of primary diseases: acute leukaemia, chronic leukaemia, malignant lymphoma, plasma cell disease, myelodysplastic syndrome / myeloproliferative neoplasm, and aplastic anaemia / bone marrow failure syndrome. According to the current survey of the European Society for Blood and Marrow Transplantation (EBMT) [8], 55% of all autologous SCTs performed in 2019 were in patients with plasma cell disease, which include multiple myeloma.

While the results of Jansen 2020 do not support the results of Rapid Report V18-02, they do not contradict them either; consequently, on the basis of studies of low informative value of results, an overall correlation between TC volume and quality of treatment outcome can be derived in favour of higher-volume TCs for autologous SCT.

7 Conclusion

For the investigation of any correlation between volume and quality of treatment outcome in allogeneic SCT (research question 1a) and autologous SCT (research question 1b), the present rapid report was able to include 1 observational study each. Both studies investigated volume solely on the TC level and quality of treatment outcome solely for the outcome of all-cause mortality.

Regarding allogeneic SCT, on the basis of 1 study of high informative value of results, the present rapid report derived a correlation between volume and quality of treatment outcome in favour of higher-volume TCs for the outcome of all-cause mortality. This result supports the conclusion of Rapid Report V18-02.

Regarding autologous SCT, the 1 study of low informative value of results did not allow the present rapid report to derive any correlation between TC volume and quality of treatment outcome. This result does not alter the conclusion of Rapid Report V18-02, which derived a correlation.

No studies were found for investigating the effects of specific minimum case numbers implemented in patient care for stem cell transplantation on the quality of treatment outcomes (research question 2).

References for English extract

Please see full rapid report for full reference list.

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7. Gratwohl A, Brand R, McGrath E et al. Use of the quality management system "JACIE" and outcome after hematopoietic stem cell transplantation. Haematologica 2014; 99(5): 908-915. https://dx.doi.org/10.3324/haematol.2013.096461.

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The full report (German version) is published under
https://www.iqwig.de/en/projects/v21-04.html

Appendix A – Search strategies

A.1 – Searches in bibliographic databases

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) 1946 to April Week 2 2021
- Ovid MEDLINE(R) Daily Update April 16, 2021

#	**Searches**
1	Bone Marrow Transplantation/
2	exp Stem Cell Transplantation/
3	(((stem adj1 cell*) or (bone adj1 marrow*) or allogeneic* or autologous* or peripheral blood progenitor cell*) adj3 transplant*).ti,ab.
4	SCT*.ti,ab.
5	or/1-4
6	((minim* or high* or low or patient or outcome* or importance*) adj3 (volume* or caseload)).ab,ti.
7	((hospital* or center* or centre* or unit* or surgeon* or provider* or physician*) adj2 (factor* or effect*)).ab,ti.
8	((hospital* or center* or centre* or unit*) adj5 (type or level or small* or size)).ab,ti.
9	((hospital* or center* or centre* or unit* or surgeon* or surgical* or physician* or provider*) adj2 (volume* or caseload* or experience* or characteristic* or performance*)).ab,ti.
10	((improve* adj2 outcome*) and (hospital* or center* or centre* or unit* or surgeon*)).ti,ab.
11	((surgeon* or surgical* or physician* or provider* or specialist*) adj3 outcome*).ti,ab.
12	(referral* adj3 (selective* or volume* or rate*)).ti,ab.
13	or/6-12
14	and/5,13
15	14 not (comment or editorial).pt.
16	15 not (exp animals/ not humans.sh.)
17	16 and 201812:3000.(dt).

Search interface: Ovid

- Ovid MEDLINE(R) Epub Ahead of Print and In-Process, In-Data-Review & Other Non-Indexed Citations April 16, 2021

#	**Searches**
1	(((stem and cell*) or (bone and marrow*) or allogeneic* or autologous* or peripheral blood progenitor cell*) and transplant*).ti,ab.
2	SCT*.ti,ab.
3	or/1-2
4	((minim* or high* or low or patient or outcome* or importance*) adj3 (volume* or caseload)).ab,ti.
5	((hospital* or center* or centre* or unit* or surgeon* or provider* or physician*) adj2 (factor* or effect*)).ab,ti.
6	((hospital* or center* or centre* or unit*) adj5 (type or level or small* or size)).ab,ti.
7	((hospital* or center* or centre* or unit* or surgeon* or surgical* or physician* or provider*) adj2 (volume* or caseload* or experience* or characteristic* or performance*)).ab,ti.
8	((improve* adj2 outcome*) and (hospital* or center* or centre* or unit* or surgeon*)).ti,ab.
9	((surgeon* or surgical* or physician* or provider* or specialist*) adj3 outcome*).ti,ab.
10	(referral* adj3 (selective* or volume* or rate*)).ti,ab.
11	or/4-10
12	and/3,11
13	12 not (comment or editorial).pt.
14	13 not (exp animals/ not humans.sh.)
15	14 and 201812:3000.(dt).

2. Embase

Search interface: Ovid

- Embase 1974 to 2021 April 16

#	**Searches**
1	exp bone marrow transplantation/
2	exp stem cell transplantation/
3	SCT*.ti,ab.
4	(((stem* adj1 cell*) or (bone* adj1 marrow*) or allogeneic* or autologous* or peripheral blood progenitor cell*) adj3 transplant*).ti,ab.
5	or/1-4
6	((minim* or high* or low or patient or outcome* or importance*) adj3 (volume* or caseload)).ab,ti.
7	((hospital* or center* or centre* or unit* or surgeon* or provider* or physician*) adj2 (factor* or effect*)).ab,ti.
8	((hospital* or center* or centre* or unit*) adj5 (type or level or small* or size)).ab,ti.
9	((hospital* or center* or centre* or unit* or surgeon* or surgical* or physician* or provider*) adj2 (volume* or caseload* or experience* or characteristic* or performance*)).ab,ti.
10	((improve* adj2 outcome*) and (hospital* or center* or centre* or unit* or surgeon*)).ti,ab.
11	((surgeon* or surgical* or physician* or provider* or specialist*) adj3 outcome*).ti,ab.
12	(referral* adj3 (selective* or volume* or rate*)).ti,ab.
13	or/6-12
14	and/5,13
15	14 not medline.cr.
16	15 not (exp animal/ not exp human/)
17	16 not (Conference Abstract or Conference Review or Editorial).pt.
18	17 and 201812:3000.(dc).

3. The Cochrane Library

Search interface: Wiley

- Cochrane Database of Systematic Reviews Issue 4 of 12, April 2021

#	**Searches**
#1	[mh ^"Bone Marrow Transplantation"]
#2	[mh "Stem Cell Transplantation"]
#3	SCT*:ti,ab
#4	(((stem* NEAR/1 cell*) or (bone* NEAR/1 marrow*) or allogeneic* or autologous* or peripheral blood progenitor cell*) NEAR/3 transplant*):ti,ab
#5	#1 or #2 or #3 or #4
#6	((minim* or high* or low or patient or outcome* or importance*) NEAR/3 (volume* or caseload)):ti,ab
#7	((hospital* or center* or centre* or unit* or surgeon* or provider* or physician*) NEAR/2 (factor* or effect*)):ti,ab
#8	((hospital* or center* or centre* or unit*) NEAR/5 (type or level or small* or size)):ti,ab
#9	((hospital* or center* or centre* or unit* or surgeon* or surgical* or physician* or provider*) NEAR/2 (volume* or caseload* or experience* or characteristic* or performance*)):ti,ab
#10	((improve* NEAR/2 outcome*) and (hospital* or center* or centre* or unit* or surgeon*)):ti,ab
#11	((surgeon* or surgical* or physician* or provider* or specialist*) NEAR/3 outcome*):ti,ab
#12	(referral* NEAR/3 (selective* or volume* or rate*)):ti,ab
#13	#6 or #7 or #8 or #9 or #10 or #11 or #12
#14	#5 and #13
#15	#14 not (*clinicaltrial*gov* or *who*trialsearch* or *clinicaltrialsregister*eu* or *anzctr*org*au* or *trialregister*nl* or *irct*ir* or *isrctn* or *controlled*trials*com* or *drks*de*):so
#16	#15 with Cochrane Library publication date Between Dec 2018 and Dec 2021, in Cochrane Reviews, Cochrane Protocols
#17	#15 with Cochrane Library publication date Between Dec 2018 and Dec 2021, in Trials

4. Health Technology Assessment Database

Search interface: INAHTA

#	**Searches**
1	Bone Marrow Transplantation[mh]
2	Stem Cell Transplantation[mhe]
3	SCT*
4	(stem cell* OR bone marrow* OR allogeneic* OR autologous* OR peripheral blood progenitor cell*) AND transplant*
5	#4 OR #3 OR #2 OR #1
6	((minimum* OR hospital*) AND volume*)
7	#6 AND #5
8	#6 AND #5 (2018 -2021)