Replication study to analyze the surgical treatment of proximal humeral fracture

Short Study Protocol

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1. Background of the Study

Age-related fragility fractures are responsible for the loss of over one million quality-adjusted life years across Europe per year, and are thus ahead of stroke and chronic lung disease. In Europe, this results in annual treatment costs of more than 1 billion euros [1]. The proximal humeral fracture is the third most common age related fracture with an incidence of approx. 290 per 100.000 population years in elderly patients [2]. Within the last decades, an increase in the use of reverse total shoulder arthroplasty was observed (RTSA) [3]. However, to date, there is no consent about the optimal surgical treatment strategy, which is also due to the fact of missing evidence for different treatment options. Only a few randomized controlled trials (RTCs) comparing RTSA with an internal fixation using locked plate fixation (LPF; most common treatment) based small sample size are available, having partly contradictory results. Based on real world data (RWD) including more than 50,000 patients, two studies analyzing the outcome after both therapies are available in the literature.

The study at hand aimed to analyze the replicability of the observed treatment effects in these studies published by Köppe et al. [3] and Stolberg-Stolberg et al. [4].

2. Population

The German reimbursement system governs the remuneration of health care services subject to encoded diagnoses (International Statistical Classification of Diseases, German Modification; ICD-10 GM) and procedures (German procedure classification – *Operationen- und Prozedurenschluessel*; OPS) by means of the 'German Diagnosis Related Groups' taxonomy (GDRG). This obligatory documentation and accounting system is specified and further regulated in detail by mandatory coding instructions.

The database consists of retrospective health claims data of the German BARMER health insurance company. This includes anonymized data from following sectors:

- Inpatient data (§301 SGB V): In addition to information on costs, duration of hospitalization and information about treating hospital, standardized information on diagnoses (coded according to ICD-10 GM) and procedures (coded according to OPS) are available.
- Outpatient data (§295 SGB V): In addition to information on costs, diagnoses (ICD-10 GM) and procedures (OPS).
- Pharmaceutical therapies (§300 SGB V): Information on medication (coded via ATC classification), as well as costs and DDD (Defined Daily Dose).

2.1. Treatment Groups and study population cohorts

The study design is in accordance to the original study with patient selection and exclusion criteria as described in Köppe et al. [3]. Thus, within an index period from January 2011 to September 2022, all patients will be included, who had an inpatient coded treatment using LPF (OPS: 5-794.21, 5-794.k1) or RTSA (OPS: 5-824.21) and no exclusion criterion as given in table 1.

Table 1: Exclusion criteria

Exclusion Criteria
Incomplete insurance status within two years before index
Incomplete basic information
Age<65 years

Missing diagnosis of PHF (ICD: S42.2) within two years before surgery
Previous surgical treatment (RTSA, LPF or other fracture fixation)
Coded polytrauma
Bone tumors/ bone metastasis
Both sides or missing information of surgery side
COVID-19 infection during index hospitalization

Patients were grouped into two treatment groups: LPF (reference group) or RTSA depending on which therapy was performed first. If RTSA and LPF were coded at the same day, patients were assigned to RTSA group. Two different analysis sets were defined as follows:

- Short-term set: including all patients.
- Long-term set: including all patients, which were discharged alive and had an index surgery before 2022 (to guarantee a possible follow-up time of a least one year).

3. Endpoints and Variables

3.1. Variables

The following table lists all variables relevant to the analysis along with their ICD, OPS or ATC codes. For each patient, possible comorbidities will be recorded at baseline by including all outpatient and inpatient information coded within two years prior to the index event (index admission). The "minor outpatient complications" defined below (see the last two rows of the following table) will be based exclusively on outpatient information coded after discharge. All other variables will be collected exclusively from inpatient information. Corresponding data sources are additionally marked in the table and explained in the footnotes.

Variable	**Classification**	**Code**
Proximal humeral fracture	ICD	S42.2
Multi-fragmented LPF	OPS	5-794.21, 5-794.k1
RTSA	OPS	5-824.21
Comorbidities at Baseline[1]		
Alcohol abuses	ICD	E24.4, F10, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K85.2, K86.0, T51.0, T51.9
Atherosclerosis	ICD	I70
Atrial fibrillation and flutter	ICD	I48
Bone tumor/metastasis	ICD	C40.0, C79.5, C79.86, C79.9
Cancer	ICD	C
Chronic kidney disease	ICD	N18, N19
Chronic polyarthritis	ICD	M05, M06
Congestive heart failure	ICD	I50
Coronary heart disease	ICD	I25
Dementia	ICD	F00, F01, F02, F051, G30, G31.1
Diabetes mellitus	ICD	E10-E14

[1] Data collection based on outpatient and inpatient information in the period of two years before the index surgery. Exception: Rotator cuff rupture.

Hypertension	ICD	I10-I15
Infection	ICD	M86.01, M86.11, M86.21, M86.31, M86.41, M86.51, M86.61, M86.81, M86.91, T84.5, T84.6, T84.7
Nicotine abuses	ICD	F17
Obesity	ICD	E66
Osteoporosis	ICD	M80-M85
Parkinson	ICD	G20
Polytrauma	ICD, OPS, DRG	ICD: T07, OPS: 5-982, or coded DRG started with "W"
Rotator cuff rupture[2]	ICD	M75.1, S46.0
Omarthrosis	ICD	M25.51
Previous stroke	ICD	I60-I69
Other fracture fixation	OPS	5-790.01, 5-790.11, 5-790.21, 5-790.31, 5-790.41, 5-790.51, 5-790.61, 5-790.71, 5-790.81, 5-790.91, 5-790.d1, 5-790.m1, 5-790.n1, 5-790.p1, 5-790.x1, 5-793.11, 5-793.21, 5-793.31, 5-793.41, 5-793.51, 5-793.61, 5-793.71, 5-793.81, 5-793.91, 5-793.a1, 5-793.b1, 5-793.c1, 5-793.g1, 5-793.k1, 5-793.m1, 5-793.n1, 5-793.x1, 5-794.01, 5-794.11,5-794.31, 5-794.41, 5-794.51, 5-794.61, 5-794.71, 5-794.81, 5-794.a1, 5-794.b1, 5-794.c1, 5-794.g1, 5-794.m1, 5-794.n1, 5-794.x1, 5-824.00, 5-824.01, 5-824.0x, 5-824.20
Pharmaceutical therapy at baseline[3]		
Analgesics[4]	ATC	N02
Antibiotics[5]	ATC	J01
Any anticoagulant	ATC	B01AA, B01AB, B01AC, B01AE, B01AF, B01AX
Vitamin D or calcium	ATC	A11CC
Bisphosphonates	ATC	M05BA, M05BB
Any osteoporosis pharmacotherapy	ATC	Vitamin D/Calcium or Bisphosphonates
General Complications		
Acute liver failure	ICD	K72.0, K72.7, K72.9
Acute myocardial infarction	ICD	I21, I22
Acute renal failure	ICD	N17
Acute respiratory distress syndrome	ICD	J80
Cardiac arrest	ICD	I46
Deep vein thrombosis	ICD	I80.1, I80.2, I82.2, I82.3
Pulmonary embolism	ICD	I26
Sepsis	ICD	A41, A40, B37.7, R65.0, R65.1, R65.9, R57.2
Hemorrhagic stroke	ICD	I60-I62
Ischemic stroke	ICD	I63-I64

[2] If only coded during index hospitalization.
[3] Data collection based medication information in the period of two years before the index surgery.
[4] Only including 14 days before admission.
[5] Only including 14 days before admission.

Delirium	ICD	F05
Resuscitation	OPS	8-77
Need of intensive care unit	OPS	8-980, 8-98f
Surgical complications		
Osteonecrosis	ICD	M87.21, M87.22, M87.32, M87.82, M87.92
Vascular injury	OPS	5-388.11, 5-388.12, 5-395.11, 5-395.12, 5-397.11, 5-397.12
	ICD (only in-hospital)	S45.0, S45.1, S55.0, S55.1
Nerve injury	OPS	5-040.1, 5-040.2, 5-040.3, 5-041.1, 5-041.2, 5-041.3, 5-044.1, 5-044.2, 5-044.3, 5-045.1, 5-045.2, 5-045.3, 5-046.1, 5-046.2, 5-046.3, 5-047.1, 5-047.2, 5-047.3, 5-048.1, 5-048.2, 5-048.3, 5-049.1, 5-049.2, 5-049.3, 5-04b.1, 5-04b.2, 5-04b.3, 5-050.1, 5-050.2, 5-050.3, 5-051.1, 5-051.2, 5-051.3, 5-052.1, 5-052.2, 5-052.3, 5-053.1, 5-053.2, 5-053.3, 5-054.1, 5-054.2, 5-054.3, 5-055.1, 5-055.2, 5-055.3, 5-056.1, 5-056.2, 5-056.3, 5-057.1, 5-057.2, 5-057.3
	ICD (only in-hospital)	S44, G45.0, S14.3
Joint damage / cartilage damage (LPF)	OPS	5-780.31, 5-784.51, 5-784.61, 5-800.80, 5-810.40, 5-812.00, 5-812.30, 5-812.90, 5-812.a0, 5-812.e0, 5-812.f0, 5-812.g0, 5-812.h0, 5-812.k0, 5-812.m0
Upper limb amputation, ipsilateral (shoulder or upper arm)	OPS	5-862.1, 5-862.2
Infection	OPS	5-780.41, 5-780.51, 5-780.61, 5-780.71, 5-780.81, 5-780.91, 5-800.20, 5-800.30, 5-800.a0, 5-800.b0, 5-810.10, 5-810.70, 5-810.80, 8-989, 8-989.0, 8-989.1, 8-989.2, 8-989.3, 8-989.4, 8-989.5, 8-989.6
	ICD (only in-hospital)	T84.5, T84.6, T84.7, M86.01, M86.11, M86.21, M86.31, M86.41, M86.51, M86.61, M86.81, M86.91
Haematoma after surgery	ICD (only in-hospital)	T81.0
Surgical incidents	ICD (only in-hospital)	Y69!, Y84.9, Y82.8
Consequences of injury of the upper extremity	ICD (only in-hospital)	T92.1
Secondary surgery, open (LPF)	OPS	5-780.01, 5-780.11, 5-780.21, 5-780.31, 5-780.61, 5-780.x1, 5-782.11, 5-782.21, 5-782.31, 5-782.41, 5-782.51, 5-782.62, 5-782.72, 5-782.82, 5-782.92, 5-782.a1, 5-784.01, 5-784.11, 5-784.21, 5-784.31, 5-784.41, 5-784.51, 5-784.61, 5-784.71, 5-784.81, 5-784.a1, 5-784.b1, 5-785.01, 5-785.11, 5-785.21, 5-785.31, 5-785.41, 5-785.51, 5-785.61, 5-785.71, 5-789.b1, 5-789.c1, 5-794.01, 5-794.11, 5-794.21, 5-794.31, 5-794.41, 5-794.71, 5-794.81, 5-794.k1, 5-800.10, 5-800.30, 5-800.40, 5-800.50, 5-800.70, 5-800.80, 5-800.90, 5-800.x0, 5-801.00, 5-801.30, 5-801.40, 5-801.b0, 5-801.c0, 5-801.g0, 5-801.h0, 5-801.k0, 5-801.m0, 5-801.n0, 5-801.p0, 5-805.0, 5-805.1, 5-805.2, 5-805.3, 5-805.4, 5-805.5, 5-805.6, 5-805.7, 5-805.8, 5-805.9, 5-805.a, 5-850.01,5-850.11, 5-850.21, 5-850.31,

		5-850.41, 5-850.51, 5-850.61, 5-850.71, 5-850.81, 5-850.91, 5-850.a1, 5-850.b1, 5-850.c1, 5-850.d1, 5-850.e1, 5-850.f1, 5-850.g1, 5-850.h1, 5-850.j1, 5-850.x1, 5-851.11, 5-851.21, 5-852.01, 5-852.11, 5-853.01, 5-853.11, 5-855.01, 5-855.11, 5-855.21, 5-855.51, 5-855.61, 5-855.71, 5-855.81, 5-855.91, 5-855.a1, 5-859.01, 5-859.11, 5-862.1, 5-862.2, 5-892.06, 5-892.07, 5-892.16, 5-892.17, 5-896.06, 5-896.16, 5-896.26
Secondary arthroscopy (LPF)	OPS	5-782.b1, 5-784.c1, 5-784.d1, 5-784.e1, 5-784.f1, 5-810.00, 5-810.10, 5-810.20, 5-810.40, 5-810.50, 5-810.70, 5-810.80,
Revision (LPF)	OPS	5-785.01, 5-785.11, 5-785.21, 5-785.51, 5-785.61, 5-785.71 5-789.31, 5-78a.01, 5-78a.11, 5-78a.21, 5-78a.31, 5-78a.41, 5-78a.51, 5-78a.61, 5-78a.71, 5-78a.90, 5-78a.c1, 5-78a.g1,
Secondary arthroplasty (LPF)	OPS	5 824.0, 5 824.20, 5 824.21
Arthrolysis (LPF)	OPS	5 800.60, 5 810.20, 5 810.90
Decompression of subacromial space (LPF)	OPS	5 814.3
Debridement (LPF)	OPS	5 819.10
Secondary surgery, open (RTSA)	OPS	5-780.01, 5-780.11, 5-780.21, 5-780.31, 5-780.61, 5-780.x1, 5-782.11, 5-782.21, 5-782.31, 5-782.41, 5-782.51, 5-782.62, 5-782.72, 5-782.82, 5-782.92, 5-782.a1, 5-785.01, 5-785.11, 5-785.21, 5-785.31, 5-785.41, 5-785.51, 5-785.61, 5-785.71, 5-789.b1, 5-791.02, 5-791.12, 5-791.22, 5-792.02, 5-792.12, 5-792.22, 5-792.k2, 5-800.10, 5-800.30, 5-800.40, 5-800.50, 5-800.70, 5-800.80, 5-800.90, 5-800.x0, 5-850.01, 5-850.11, 5-850.21, 5-850.31, 5-850.41, 5-850.51, 5-850.61, 5-850.71, 5-850.81, 5-850.91, 5-850.a1, 5-850.b1, 5-850.c1, 5-850.d1, 5-850.e1, 5-850.f1, 5-850.g1, 5-850.h1, 5-850.j1, 5-850.x1, 5-859.01, 5-859.11, 5-862.1, 5-862.2, 5-892.06, 5-892.07, 5-892.16, 5-892.17, 5-896.06, 5-896.16, 5-896.26
Secondary arthroscopy (RTSA)	OPS	5-782.b1, 5-810.00, 5-810.10, 5-810.20, 5-810.40, 5-810.50, 5-810.70, 5-810.80, 5-810.90, 5-811.20, 5-811.30, 5-811.40, 5-814.b, 5-814.c, 5-814.d, 5-814.e, 5-819.00, 5-819.10, 5-819.20
Revision (RTSA)	OPS	5-785.01, 5-785.11, 5-787.01, 5-787.11, 5-787.21, 5-787.31, 5-787.k1, 5-789.31, 5-78a.01, 5-78a.11, 5-78a.21, 5-78a.k1, 5-810.40, 5-824.21, 5-825.00, 5-825.1 (only 2010-2012), 5-825.21, 5-825.8, 5-825.k, 5-825.k0, 5-825.k1, 5-825.kx
Resection arthroplasty (for spacer placement)	OPS	5 829.3
Impingement	ICD (only in-hospital)	M75.4
Implant dislocation	ICD (only in-hospital)	T84.10, T84.00
Bursitis	ICD (only in-hospital)	M75.5
Compartment syndrome	ICD (only in-hospital)	S41.86!
Consequences of injury of the upper extremity	ICD (only in-hospital)	T92.1

Minor outpatient complications (LPF) [6]	ICD	G56.1, G56.2, G56.3, I80.80, I80.81, M00.01, M00.11, M00.21, M00.81, M00.91, M13.11, M13.81, M13.91, M19.11, M24.01, M24.11, M24.21, M24.41, M24.31, M24.51, M24.61, M25.11, M25.21, M25.31, M25.41, M25.51, M25.61, M25.71, M61.01, M62.21, M62.22, M62.41, M62.51, M62.61, M65.81, M65.91, M75.0, M75.1, M75.2, M75.4, M75.5, M84.21, M84.31, M86.01, M86.11, M86.21, M86.31, M86.41, M86.51, M86.61, M86.81, M86.91, M87.21, M87.22M87.31, M87.81, M87.91, M89.51, M96.6, T79.60, T84.10, T84.5, T84.6, T84.7
Minor outpatient complications (RTSA) [7]	ICD	G56.1, G56.2, G56.3, I80.80, I80.81, M00.01, M00.11, M00.21, M00.81, M00.91, M24.21, M24.41, M24.31, M24.51, M24.61, M25.11, M25.21, M25.31, M25.41, M25.51, M25.61, M25.71, M61.01, M62.21, M62.41, M62.51, M62.61, M65.81, M65.91, M75.0, M75.1, M75.2, M75.4, M75.5, M84.31, M86.01, M86.11, M86.21, M86.31, M86.41, M86.51, M86.61, M86.81, M86.91, M96.6, T79.60, T81.4, T84.5, T84.6, T84.7, T84.00
Classification of complications		
General complications during hospital stay	Myocardial infarction, thrombo-embolic events, acute renal failure, acute liver failure, ARDS, sepsis, delirium, need of intensive care, resuscitation	
Surgical complications during hospital stay	Infection, bursitis, compartment syndrome Consequences of injury of the upper extremity, haematoma after surgery, impingement, implant dislocation, mechanical malfunction or material failure/loosening, peri-prosthetic or peri-implant fracture nerve injury, vascular trauma	
Implant-associated complications during hospital stay	Impingement, bursitis, mechanical malfunction or material failure/loosening, peri-prosthetic or peri-implant fracture	
Non-implant associated complications during hospital stay	Infection, infection with antibiotic-resistant germs, haematoma after surgery	
Major adverse event (MAE)	resuscitation, cardiac arrest, myocardial infarction, stroke, acute renal failure, acute liver failure, acute respiratory distress syndrome, sepsis or death from any case	
Thromboembolic event	Deep vein thrombosis, pulmonary embolism, ischemic stroke	
Surgical complications after discharge	Adhesive capsulitis, arthrolysis, debridement, decompression of subacromial space, frozen shoulder, infection, infection with antibiotic-resistant germs, joint damage/cartilage damage, luxation, delayed union, non-union/ pseudoarthrosis, malunion, nerve injury, vascular injury, osteonecrosis, postoperative stiffness, secondary arthroplasty, secondary arthroscopy, secondary surgery (open) including revision surgery, upper limb amputation	

[6] Data collection exclusively based on outpatient information coded after discharge.
[7] Data collection exclusively based on outpatient information coded after discharge.

3.2. Endpoints

The following two sub-chapters list the primary and secondary endpoints to be analyzed together with their definition. For more information, as well as underlying ICP, OPS and ATC codes, see Chapter 3.1.

3.2.1. Primary Endpoints

Variable	Definition
30-day mortality	Death from any cause during the first 30-days after surgery.
Overall survival (OS)	- Time from discharge of index hospitalization to death of any case. - Death will be determined using the coded death as the reason for withdrawal in the BARMER database. In addition, all inpatient cases will be reviewed during follow-up, to determine whether death was reported as the reason for discharge.
Major adverse events during index case	See above, only events during hospitalization
Major adverse events after discharge	- Time from discharge of index hospitalization to MAE as defined above
Thromboembolic events during index case	See above, only events during hospitalization
Thromboembolic events (or death) after discharge	- Time from discharge of index hospitalization to a thromboembolic event or death of any case.
Surgical complications during index case	See above, only events during hospitalization
Surgical complications after discharge	- Time from discharge of index hospitalization to surgical complications, with death being considered as a competing risk event.

3.2.2. Secondary Endpoints

Implant-associated complication during index	See above, only events during hospitalization
Non-Implant-associated complication during index	See above, only events during hospitalization
Minor outpatient complications after discharge	- Time from discharge of index hospitalization to minor outpatient complications, with death being considered as a competing risk event.

4. Statistical Methods

4.1. Descriptive Statistics of Baseline Variables

Baseline variables as given by patients comorbidities, prior medications and general demographic data will be analyzed descriptively using absolute values and ratio for categorical variables and standard measures (median, mean, variance, 25%-quartile, 75%-quartile, minimum and maximum) for continuous variables).

4.2. Analysis of Primary Endpoints

To avoid bias due to differences in the distribution of insurance holders of both companies (BARMER cohort is older and had a higher proportion of women compared to German population), a propensity score matching (1:1) will be made to define the analysis set for all primary and secondary endpoints.

Matching will include year of surgery, sex, age at surgery and all listed comorbidities at baseline. Risk differences between treatment group (RTSA) and control (LPF), Z differences and sum of squared Z-differences will be reported to evaluate the balance between both treatment groups. The dependence of the matching pairs will be considered via stratified analyses for all endpoints.

4.2.1 Short-term outcomes

For all endpoints, absolute number of complications and the proportion in percent will be determined and presented. Furthermore, a 95% Clopper-Pearson confidence interval will be estimated for the proportions. However, no tests will be performed for the univariate differences between LPF and RTSA. In accordance to the models presented in Köppe et al. [3], a multivariable logistic regression model including age, sex, year of surgery, treatment group, comorbidities at baseline and prior medication will be performed to determine treatment effect of the replication cohort. For short-term analysis, all patients will be included.

4.2.1 long-term outcomes

As stated above, long-term endpoints will only considered using long-term analysis set. Patients will be observed from discharge to the end of study. Only complete matching pairs will be included to the analysis, i.e. if one of the matching partners will be excluded due to in-hospital death, the related partner will be also excluded from long-term analysis. For all endpoints, event rates one and five years after discharge will be determined by cumulative incidence function using Aalen-Johansen estimate. Rates will be presented with related 95% confidence interval. Multivariable Cox regression models will analyze the impact of baseline variables on the endpoints. The resulting hazard ratios will be presented along with the related 95% confidence intervals. In the case of competing risks, cumulative incidence function determined by Aalen-Johansen estimate and sub-distributional hazards using Fine & Gray Cox models will be calculated. Multivariable models will include the treatment group, age, sex, year of surgery, comorbidities (listed in chapter 3.1), previous medications and in-hospital outcome parameter. Moreover, two time-dependent variables were included to account for COVID-19 pandemic (variable one: represent the start of pandemic situation in Germany, variable two: coded COVID-19 infection).

Moreover, as sensitivity analysis further analysis will be performed:

- Considering a COVID-19 infection as a competing risk event for all long-term endpoints.
- Using a subset of patients, given by those with an index surgery up to 2019 and an end of follow-up defined as 31.12.2019.

4.3. Analyzing replicability

To check the replicability of the observed treatment effects by Köppe et al. [3] and Stolberg-Stolberg et al. [4] the following agreements metrics will be analyzed:

- Regulatory agreement (also known as two-trial rule): fulfilled, if original effect and replication effect have the same direction and the same significance. For an original null effect, the replication effect must also not have reached significance.
- Analyzing standardized differences.
- One-sided skeptical p-values [5].
- Meta-analysis: a meta-analysis using fixed-effects models will be performed. Even if the inter-study heterogeneity is very high (with disjoint confidence intervals of the individual studies this is the case), a meta-analysis allowing random effects does not provide any useful insights. As the inter-study variance is calculated using only two studies (OES and RES), it leads to a very

high, uninformative dispersion of the estimate. The joint effect combing original effect size (OES) and replication effect size (RES) has to be significant to fulfill statistical agreement. For an original null effect, the joint effect must also not have reached significance.

- Grade of replication as recommend by Errington et al. [6]: Five criteria will be checked and the grade of replication (0 – 5) will be presented. There are defined as:
    - Direction and significance: A null hypothesis is used to test, if the replication effect would unlikely occur under null. This property is equivalent to regulatory agreement.
    - RES is enclosed to the 95% CI of OES, also called estimated agreement.
    - OES is enclosed to the 95% CI of RES.
    - RES is enclosed to the 95% prediction interval.
    - Meta-analysis combing both is significant (or also not significant for original null effects).

5. Treatment of Missing Values

Missing values or inconsistent data in sex, day of birth, exit date of database lead to exclusion from study. Missing values are possible for the primary endpoint “30-day mortality”, since no information about death for patients with shorter follow-up period without event (censored within 30-days after surgery) will be available. Analysis will be made using all patients without missing values; an imputation will not be performed.

For all other variables, no missing data will occur in the study, since all variables are defined by existing ICD/OPS or ATC codes. If no related code will be found, the according variable will be set to zero. Since the considered comorbidities are highly relevant for any imbursement, it is very unlikely that they are not coded in the database. However, there could be a bias by setting all the variables as known variables.

6. Software

All statistical analyses will be performed using SAS (SAS Enterprise Guide Version 8.3, SAS Institute Inc., Cary, NC, USA) and R version 4.2.1, R foundation, Vienna, Austria.

7. References

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