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Aspekte der Versorgungsforschung entzündlich-rheumatischer Erkrankungen in Deutschland

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Abkürzungsverzeichnis

ADAPTHERA	Risikoadaptierte Rheumatherapie
AS	Ankylosierende Spondylitis
ASAS	Assessment Of Spondyloarthritis International Society
AUC	Area Under The Curve
bDMARDs	biologic Disease Modifying Anti-Rheumatic Drugs
BSG	Blutsenkungsgeschwindigkeit
CAPEA	Course And Prognosis of Early Arthritis
CED	Chronisch-Entzündliche Darmerkrankung
CRP	C-Reaktives Protein
csDMARDs	konventionelle, synthetische Disease Modifying Anti-Rheumatic Drugs
DGRh	Deutschen Gesellschaft Für Rheumatologie
DIVERS	Diagnostic Accuracy Of Inflammatory Back Pain Study
DMARDs	Disease Modifying Anti-Rheumatic Drugs
DRFZ	Deutsches Rheuma-Forschungszentrum Berlin
EULAR	European Alliance Of Associations For Rheumatology
HLA-B27	Human Leukocyte Antigen-B, Variante 27
IBP	Inflammatory Back Pain
ICD-10	International Classification Of Diseases, 10th Revision
KI	Konfidenzintervall
MRT	Magnetresonanz-Tomographie
nr-axSpA	Nicht-Radiographische axSpA
NSAR	Nicht-Steroidale Anti-Rheumatika
OPTIREF	Optimal Referral Strategy For Early Diagnosis Of Axial Spondyloarthritis
PD	Parodontitis
PPV	Positiver Prädiktiver Wert

PROCLAIR	Linking Patient-Reported Outcomes With Claims Data For Health Services Research In Rheumatology
PsA	Psoriasis-Arthritis
RA	Rheumatoide Arthritis
RABBIT	Rheumatoide Arthritis: Beobachtung der Biologika-Therapie
Rheuma-VOR	Verbesserung Der Rheumatologischen Versorgungsqualität Durch Koordinierte Kooperation
ROC	Receiver Operator Characteristic
SLE	Systemischer Lupus Erythematodes
SpA	Spondyloarthritis
tsDMARDs	targeted synthetic Disease Modifying Anti-Rheumatic Drugs

1. Einleitung

Entzündlich-rheumatische Erkrankungen (auch als „Rheuma“ bezeichnet) sind eine Volkskrankheit. In einer 2023 veröffentlichten systematischen Übersichtsarbeit schätzten Albrecht et al. die Anzahl der Betroffenen auf 1,5 bis 2,0 Millionen Erwachsene in Deutschland (1). Das entspricht einer Prävalenz von 2,2 bis 3,0 %. Damit sind entzündlich-rheumatische Erkrankungen genau wie beispielsweise der Diabetes Mellitus mit einer Prävalenz von 9,7 % (2) klar versorgungsrelevant. Besonders von der häufigsten entzündlich-rheumatischen Erkrankung, der rheumatoiden Arthritis (RA), sind ältere Personen häufiger betroffen. Durch die Alterung der Gesellschaft in Deutschland ist daher abzusehen, dass der schon beobachtete Prävalenzanstieg (3) sich in Zukunft noch verstärken wird.

1.1. Untersuchte Erkrankungen

In diesem Kapitel werden jeweils kurz die drei Krankheitsbilder skizziert, zu deren Diagnose, Identifikation, Versorgung und Komorbiditäten in den Originalarbeiten in Kapitel 2 geforscht wurde.

1.1.1. Rheumatoide Arthritis

Die RA ist eine Autoimmunerkrankung, die durch Entzündung in den Gelenken geprägt ist. Typisch ist ein Krankheitsbeginn im Alter von 45 bis 70 Jahren, wie Daten aus der Kerndokumentation der regionalen kooperativen Rheumazentren am Deutschen Rheuma-Forschungszentrum Berlin (DRFZ) zeigen (9) (Abbildung 1).

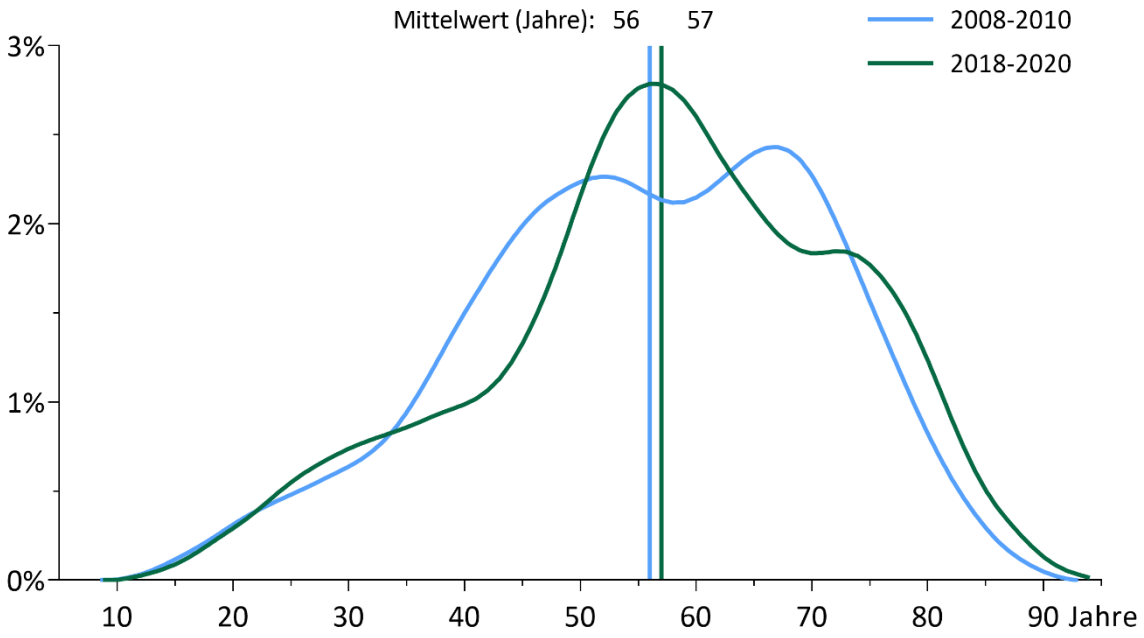

Abbildung 2: Erkrankungsalter von N=2.022 RA Patient*innen (2018-2020) (Symptomdauer ≤ 5 Jahre), Daten aus der Kerndokumentation, eigene Abbildung modifiziert nach (9).

Die Krankheit beginnt oft mit Schmerzen in den Finger- oder Zehengelenken, aber auch große Gelenke wie z.B. das Kniegelenk können betroffen sein. Weitere typische Symptome sind Morgensteifigkeit insbesondere der Hände, Fatigue, hohe Entzündungsparameter gemessen an der Blutsenkungsgeschwindigkeit (BSG) bzw. dem C-reaktiven Protein (CRP) und Schlafstörungen. Unbehandelt kann die RA durch die anhaltende Entzündung zur Gelenkzerstörung führen.

Neben erhöhten Entzündungsparametern ist bei einem Teil der Patient*innen sog. Rheumafaktor im Blut nachweisbar. Der Rheumafaktor kann auch bei Gesunden vorkommen sowie bei anderen Erkrankungen. Rheumafaktor-positiv getestete haben eine schlechtere Prognose für den Verlauf der Erkrankung (13). Spezifischer sind Antikörper gegen cyclische citrullinierte Peptide (ACPA). Ist der Test auf Rheumafaktor oder ACPA positiv, spricht man von seropositiver RA. Wegen des Einflusses auf die Prognose können therapeutische Konsequenzen daraus entstehen, ob jemand seropositive oder seronegative RA hat. Das ist ein Grund, warum in der International Classification of Diseases, 10th revision (ICD-10) die seropositive RA mit M05 anders codiert wird als die seronegative RA (M06). In der

Arbeit Nutzen von Krankenkassen-Abrechnungsdaten für die Identifikation von Personen mit rheumatoider Arthritis wird untersucht, wie gut diese ICD-10 Codes mit einer patientenberichteten Diagnose der RA übereinstimmen.

In den Behandlungsempfehlungen der EULAR (4) wird eine Behandlung so schnell wie möglich nach Diagnosestellung empfohlen. Die Pharmakotherapie ist eine wichtige Form der Behandlung der RA. Während physikalische Therapie, Rehabilitation, Bewegung und Ernährungsumstellung eine unterstützende Wirkung haben können, fußt die Therapie hauptsächlich auf sog. DMARDs. Hier wird unterschieden zwischen:

- konventionellen, synthetischen DMARDs (csDMARDs, z.B. Methotrexat, Sulfasalazin, Hydroxychloroquin, Leflunomid)
- biologischen DMARDs/Biologika (bDMARDs, z.B. Adalimumab, Certolizumab, Etanercept, Rituximab)
- targeted synthetic DMARDs (tsDMARDs, z.B. Baricitinib, Tofacitinib).

Diese Medikamentengruppen unterscheiden sich in ihren Wirkmechanismen, ihrer Verfügbarkeit und ihren Kosten. CsDMARDs sind kostengünstig und langjährig erprobt. Sie werden als erste Therapie der Wahl empfohlen, wenn eine RA diagnostiziert worden ist (4). Erst wenn sich zeigt, dass durch diese Therapie keine ausreichende Kontrolle der Krankheitsaktivität erfolgt, kann die Therapie mit einem bDMARD oder tsDMARD begonnen werden.

Durch die der RA zugrundeliegende Entzündung geht die Erkrankung mit vielen Komorbiditäten einher. Das Risiko, an kardiovaskulären Komorbiditäten (14-16), Depression (17, 18) und Osteoporose (17, 19) zu erkranken ist für Personen mit RA stark erhöht. Die Entzündung kann aber auch gemeinsame Ursache für RA und Parodontitis sein (20). Einige Studien haben eine Verbindung von RA und Parodontitis gezeigt (21, 22). Es gibt Hinweise, dass schwere Parodontitis mit Entzündungsparametern der RA assoziiert ist und sich somit auch auf Scores für Krankheitsaktivität der RA auswirken kann (23). Dies unterstreicht die Relevanz, das Vorhandensein von Parodontitis in epidemiologischen

Kohortenstudien an Personen mit RA zu erheben. In der Arbeit Parodontitis bei Patienten mit rheumatoider Arthritis wird ein Fragenkatalog untersucht, mit dem das Vorhandensein einer Parodontitis vorhergesagt werden kann- auf Basis patientenberichteter Angaben.

1.1.2. Axiale Spondyloarthritis

Die axiale Spondyloarthritis (axSpA) beginnt häufig vor dem 45. Lebensjahr, das mittlere Erkrankungsalter gemessen an 352 Patient*innen in der Kerndokumentation (Daten von 2018 bis 2020) betrug 36 Jahre (9). Das Leitsymptom sind Schmerzen im unteren Rücken. Die hohe Prävalenz von Schmerzen im unteren Rücken in der Bevölkerung (24) trägt dazu bei, dass die Krankheit oft lange unerkannt bleibt.

Die Therapieoptionen unterscheiden sich von denen der RA. Zum einen ist die physikalische Therapie eine wichtige Säule der Behandlung der axSpA (25, 26). Sie trägt entscheidend dazu bei, die Beweglichkeit zu erhalten. Zum anderen sind nicht-steroidale Anti-Rheumatika (NSAR) eine weitere wichtige Säule der Therapie. Gutes Ansprechen auf die Therapie mit NSAR ist so charakteristisch für die Erkrankung, dass es sogar in die Klassifikationskriterien der axSpA aufgenommen wurde (27). Bei unzureichendem Ansprechen auf eine Therapie mit NSAR gibt es bDMARDs und tsDMARDs, die zur Therapie der axSpA zugelassen sind.

Die Behandlung der axSpA sollte von einem Rheumatologen oder einer Rheumatologin koordiniert werden (26).

Die Krankheit manifestiert sich als Entzündung und später auch Verknöcherungen der Sakroiliakalgelenke. Ist eine radiographische Veränderung in bestimmter Stärke in den Sakroiliakalgelenken nachweisbar, spricht man von radiographischer axSpA (auch ankylosierende Spondylitis), sind noch keine (starken) Veränderungen im Röntgenbild sichtbar, aber eine Entzündung per Magnetresonanz-Tomographie (MRT) sichtbar, spricht man von nicht radiographischer axSpA (nr-axSpA). Neben den Entzündungen und Verknöcherungen der Gelenke gibt es auch sog. extra-artikuläre Manifestationen der axSpA. Zu dienen zählen die Psoriasis, chronisch-entzündliche Darmerkrankungen

wie Morbus Crohn und Colitis Ulcerosa und die Uveitis (27). Diese erfordern eine interdisziplinäre Behandlung der Erkrankung gemeinsam mit der Dermatologie, Gastroenterologie und Ophtalmologie.

Die axSpA hat bei Männern und Frauen unterschiedliche Ausprägungen. Während sie Männern und Frauen gleich häufig vorkommt, haben Männer häufiger radiographische Schäden (28), die ankylosierende Spondylitis ist also häufiger bei Männern. Das hat in der Vergangenheit dazu geführt, dass die ankylosierende Spondylitis als „Männerkrankheit“ galt (28). Das könnte zu unterschiedlichen Diagnoseverläufen bei Männern und Frauen geführt haben. Wie groß die Diagnoseverzögerung bei axSpA Patient*innen in Deutschland ist und welche Charakteristika mit einer großen Diagnoseverzögerung einhergehen wird in der Arbeit Zeitverzögerung bis zur Diagnosestellung axialer Spondyloarthritis untersucht.

1.1.3. Systemischer Lupus Erythematodes

Der systemische Lupus erythematodes (SLE) ist eine der seltenen entzündlich-rheumatischen Erkrankungen. Die Erkrankung ist eine Kollagenose, d.h. das Bindegewebe ist von der Erkrankung betroffen. SLE ist eine komplexe Erkrankung, bei der viele Organsysteme betroffen sein können. Spezifische Symptome umfassen:

- Den Bewegungsapparat (durch Entzündung der Skelettmuskulatur, Myositis, und Entzündung der Gelenke, Arthritis)
- Die Haut (charakteristisch ist hier das sog. Schmetterlingserythem, eine Rötung der Nase und Wangen)
- Kardiologische Symptome
- Pulmonale Symptome
- Die Nieren (insb. Lupus-Nephritis)
- Das Blutbild
- Neurologische Symptome (z.B. Depression, Lupus-Kopfschmerz)

Der SLE kann viele Organmanifestationen haben, die Abgrenzung zur Komorbidität ist nicht immer klar möglich. Wie häufig bestimmte Manifestationen auftreten und der zeitliche Ablauf des Auftretens von Organmanifestationen bzw. Komorbiditäten nach einer inzidenten SLE-Diagnose wird in der Arbeit Komorbiditäten bei systemischem Lupus erythematodes untersucht.

Die Diagnose ist komplex und wird mithilfe differenzierter Antikörper-Diagnostik gestellt (29). Bei der Behandlung des SLE gibt es deutlich weniger Therapieoptionen als beispielsweise bei der RA.

Hydroxychloroquin wird neben der Gabe von Glukokortikoiden als Mittel der Wahl für die Therapie empfohlen (30). Gelingt es damit nicht, Remission zu erreichen, stehen die bDMARDs Belimumab, Anifrolumab und Rituximab zur Verfügung.

Betroffen sind von der Erkrankung überwiegend Frauen, in der Kerndokumentation betrug in 2020 der Frauenanteil bei SLE 87% (9).

1.2. Herausforderungen in der Versorgung entzündlich-rheumatischer Erkrankungen in Deutschland

Alle Betroffenen entzündlich-rheumatischer Erkrankungen sollten fachärztlich rheumatologisch versorgt werden (4). Dass eine allgemeinmedizinische Versorgung oft nicht ausreicht, zeigt die deutlich niedrigere Versorgung von RA-Patient*innen mit disease modifying anti-rheumatic drugs (DMARDs) als in der fachärztlichen Versorgung (3, 5). In der Studie von Steffen et al. (6) hatten rheumatologisch Versorgte ein Odds Ratio von 5,9 im Vergleich zu allgemeinärztlich Versorgten, ein konventionelles, synthetisches DMARD (csDMARD) zu erhalten.

Die fachärztlich rheumatologisch geleitete Versorgung kann in Deutschland aktuell jedoch nicht gewährleistet werden. Im Memorandum der Deutschen Gesellschaft für Rheumatologie (DGRh) zur Versorgungsqualität in der Rheumatologie von 2017 (7) erläutern Zink et al., dass es allein in der ambulanten Versorgung einen Mehrbedarf an 574 Rheumatolog*innen gibt. Dieser Mangel an rheumatologischer Versorgung trägt dazu bei, dass es sehr schwierig sein kann, einen Termin zur

fachärztlichen Abklärung einer Verdachtsdiagnose zu bekommen. Die Situation wird sich aufgrund der Altersstruktur der Rheumatolog*innen noch verschärfen- es waren Stand 2019 mehr Rheumatolog*innen im Rentenalter als unter 40-Jährige ärztlich tätig (8).

Gerade auch für den Teil der Betroffenen, die nicht in Großstädten leben ist der Besuch in der Rheuma-Praxis oder Ambulanz schwieriger umzusetzen. Daten aus der Kerndokumentation (9) zeigen, dass Patient*innen mit ländlichem Wohnort im Mittel 51 km fahren müssen, während es bei in der Großstadt wohnenden nur 23 km sind.

Nicht nur zur Behandlung, sondern auch zur Diagnose einer entzündlich-rheumatischen Erkrankung ist fachärztliche Expertise unverzichtbar. Es handelt sich um komplexe Krankheitsbilder, die oft schwierig zu diagnostizieren sind. Dabei ist insbesondere bei der RA eine frühe Behandlung wichtig, um Langzeitfolgen zu vermeiden. Das sog. „Window of opportunity“ für den Start der Behandlung nach Symptombeginn beträgt hier nur ca. 12 Wochen (10, 11). Wird später mit der medikamentösen Therapie begonnen, kann dies zu irreversiblen negativen Folgen für den Krankheitsverlauf führen. Im Kapitel „Zeitverzögerung bis zur Diagnosestellung axialer Spondyloarthritis“ wurde untersucht, wie lange es im Mittel dauert, bis die Diagnose einer axSpA bei Versicherten der Barmer Krankenversicherung gestellt ist.

Es gibt verschiedene Ansätze, um eine zeitnahe Versorgung nach Krankheitsbeginn zu gewährleisten. Eine Schlüsselrolle spielen dabei die ersten Ansprechpersonen bei körperlichen Beschwerden: hausärztlich tätige Ärzt*innen. Um diesen eine Hilfestellung zu geben, wann eine rheumatologische Abklärung von Symptomen wie Gelenkbeschwerden oder Rückenschmerzen sinnvoll ist, gibt es verschiedene Sets an Klassifikationskriterien. Diese können eine Diagnose nicht ersetzen, geben aber wichtige Hinweise auf das Vorliegen einer bestimmten Erkrankung. Für die RA wurden z.B. die Klassifikationskriterien des American College of Rheumatology (ACR) und der European Alliance of Associations for Rheumatology (EULAR) entwickelt (12). Personen, die diese Kriterien erfüllen können ggf. auch in der hausärztlichen Versorgung eine RA-Diagnose erhalten. Für den entzündlichen

Rückenschmerz wurden verschiedene Kriteriensets entwickelt, die in der Arbeit Kriterien entzündlichen Rückenschmerzes bei der Diagnose einer axialen Spondyloarthritis genutzt werden.

2. Eigene Arbeiten

2.1. Zeitverzögerung bis zur Diagnosestellung axialer Spondyloarthritis

Die Bedeutung einer frühen Diagnose entzündlich-rheumatischer Erkrankungen wurde in der Einleitung am Beispiel der RA bereits dargelegt. Auch bei der axSpA spielt eine zügige Diagnose eine wichtige Rolle für den weiteren Krankheitsverlauf. In Deutschland wurde 2007 von Brandt et al. (31) die mediane Zeit von Symptombeginn bis zu einer axSpA-Diagnose in 159 Betroffenen mit 5,0 Jahren angegeben. Ziel der folgenden Arbeit war es zu untersuchen, ob es seitdem Verbesserungen in der Diagnoseverzögerung gegeben hat. Weiterhin wurde analysiert, ob es einen Zusammenhang der Diagnoseverzögerung zu klinischen oder soziodemographischen Merkmalen gab.

Der nachfolgende Text entspricht dem Abstrakt der Arbeit:

Redeker I, Callhoff J, Hoffmann F, Haibel H, Sieper J, Zink A, et al. Determinants of diagnostic delay in axial spondyloarthritis: an analysis based on linked claims and patient-reported survey data. Rheumatology (Oxford). 2019;58(9):1634-8.
https://doi.org/10.1093/rheumatology/kez090

Abstract

Objectives. The objective of this study was to assess the current diagnostic delay in axial SpA (axSpA) and to analyse factors associated with it.

Methods. A stratified sample of subjects with a diagnosis of axSpA (International Classification of Diseases, 10th Revision code M45) was drawn from health insurance data in Germany and was questioned on disease-related, lifestyle and socio-economic characteristics. The diagnostic delay was calculated as the time from back pain onset until a diagnosis of axSpA. A multivariable linear regression analysis was performed to explore factors associated with the diagnostic delay.

Results. Among 1677 patients with axSpA included in the analysis, the mean diagnostic delay was 5.7 years (median 2.3). Of those, 407 patients were diagnosed in 1996-2005 and 484 patients in 2006-2015. The mean diagnostic delay was not substantially different in both periods: 6.3 years (median 2.6) and 7.4 (2.7), respectively. Multivariable linear regression revealed that female sex [b = 1.85 (95% CI 1.06, 2.65)], negative HLA-B27 status [b = 3.61 (95% CI 2.07, 5.14)], presence of psoriasis [b = 1.40 (95% CI 0.08, 2.73)] and younger age at symptom onset [b = 1.91 (95% CI 1.53, 2.29)] were factors associated with a longer diagnostic delay.

Conclusion. The diagnostic delay in axSpA is still unacceptably long. Patients who are female, young at symptom onset, HLA-B27 negative or have psoriasis have a longer diagnostic delay. Specific referral strategies might be necessary in order to decrease the diagnostic delay in patients presenting with these characteristics.

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Concise report

Determinants of diagnostic delay in axial spondyloarthritis: an analysis based on linked claims and patient-reported survey data

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Abstract

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Conclusion. The diagnostic delay in axSpA is still unacceptably long. Patients who are female, young at symptom onset, HLA-B27 negative or have psoriasis have a longer diagnostic delay. Specific referral strategies might be necessary in order to decrease the diagnostic delay in patients presenting with these characteristics.

Key words: axial spondyloarthritis, diagnostic delay

CLINICAL SCIENCE

Rheumatology key messages

- The diagnostic delay of 5.7 years in axial spondyloarthritis is still unacceptably long.
- Diagnostic delay in axial spondyloarthritis is associated with HLA-B27 negativity, female sex, psoriasis and younger age at onset.
- Specific referral strategies might be necessary to decrease the delay in certain subpopulations of axial spondyloarthritis.

Introduction

Axial SpA (axSpA) is a chronic inflammatory disease primarily affecting the axial skeleton, i.e. SI joints and/or spine [1]. Worldwide, the diagnosis of axSpA is usually delayed. A decade ago, a delay of 5–10 years was reported [2]. However, early diagnosis of axSpA is crucial in order to achieve an optimal treatment response [3, 4] and is likely to contribute to prevention of structural damage in the spine [5, 6]. Prior to the introduction of the Assessment of Spondyloarthritis International Society criteria in 2009 [7], diagnosis and classification of axSpA relied heavily on the presence of X-ray changes in the SI joints or spine and therefore patients with early disease were missed. The inclusion of MRI of the SI joints in the diagnostic approach [8] in patients with suspected

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axSpA allows for disease recognition during the initial stages of the disease. Little is known about whether a reduction in diagnostic delay has occurred in recent years.

The objective of this study was to explore the diagnostic delay and to analyse factors associated with the delay in a large nationwide group of persons with axSpA.

Methods

Study design

The present study was conducted within the Linking Patient-Reported Outcomes with CLAIms data for health services research in Rheumatology (PROCLAIR) network [9]. A detailed description of the patient selection process has been reported elsewhere [9]. Briefly, a random sample, stratified by age and sex, of 5000 persons with an axSpA diagnosis [International Classification of Diseases, 10th Revision, German Modification (ICD-10-GM) code M45] was drawn from claims data of one of the two largest nationwide statutory health insurance funds (BARMER). In 2015, all selected persons received a questionnaire on demographic, socio-economic and SpA-related parameters, including the date of SpA-related symptom onset and the date of the diagnosis. Patients' written informed consent on the linkage of data derived from questionnaire and claims data was obtained in all cases and the study was approved by the ethics committee of the Charité – Universitätsmedizin Berlin, Berlin, Germany.

Statistical analysis

Weighted subgroup analyses according to the sex and age distribution of the source population were performed on those who confirmed their axSpA diagnosis. Descriptive statistics [means, S.E.M.s, medians, tertiles, interquartile ranges (IQRs) and percentages] were used to characterize the study population. S.E.M. was used as an appropriate measure of the certainty of estimation for the means in the stratified sample. The difference between the age at axSpA diagnosis and age at symptom (back pain) onset was referred to as the diagnostic delay. The median diagnostic delay in the entire group was used as a threshold for defining two groups of axSpA patients with a short or long diagnostic delay. Differences between the groups were assessed using one-way analysis of variance for continuous variables and using Rao–Scott χ^2 tests otherwise. Tests resulting in P-values <0.05 were considered statistically significant. In a further analysis, patients in the lowest tertile of diagnostic delay were compared with those in the highest tertile of diagnostic delay.

In order to investigate whether there was a change in diagnostic delay over time, we additionally analysed the delay among patients who received an axSpA diagnosis in the last two decades: between 1996 and 2005 and between 2006 and 2015.

Univariable and stepwise multivariable linear regression analyses were used to determine factors associated with diagnostic delay in persons with axSpA, with a focus on explanations, including the variables sex; age at symptom onset; HLA-B27 status; presence of psoriasis, uveitis or IBD and education level. A significance level of 0.05 was required to allow a variable into the model and a significance level of 0.05 was required for a variable to stay in the multivariable model. Age at symptom onset and sex were always included in the model. Parameter estimates (β) were calculated with a 95% CI.

Data analyses were performed with SAS 9.4 (SAS Institute, Cary, NC, USA) using procedures for complex survey designs.

Results

Of 4471 persons (original sample of 5000 persons minus those who had changed their insurance or died) who received the questionnaire, a total of 2082 persons (47%) responded and gave their consent for linking questionnaire data to claims data. Of those, 1776 persons confirmed their axSpA diagnosis via questionnaire (85%) [9] and 1677 persons reported the date of symptom onset and the date of diagnosis and were therefore included in the final analysis set. In the entire group of 1677 patients with a confirmed axSpA diagnosis, the mean diagnostic delay was 5.7 years (S.D. 0.2) and the median diagnostic delay was 2.3 years (IQR 0.1–7.2).

The main demographic and disease-related characteristics of these patients are presented in Supplementary Table S1, available at *Rheumatology* online. All variables obtained from questionnaire data had a maximum of missing values of 4%, except for HLA-B27 status (31% missing values).

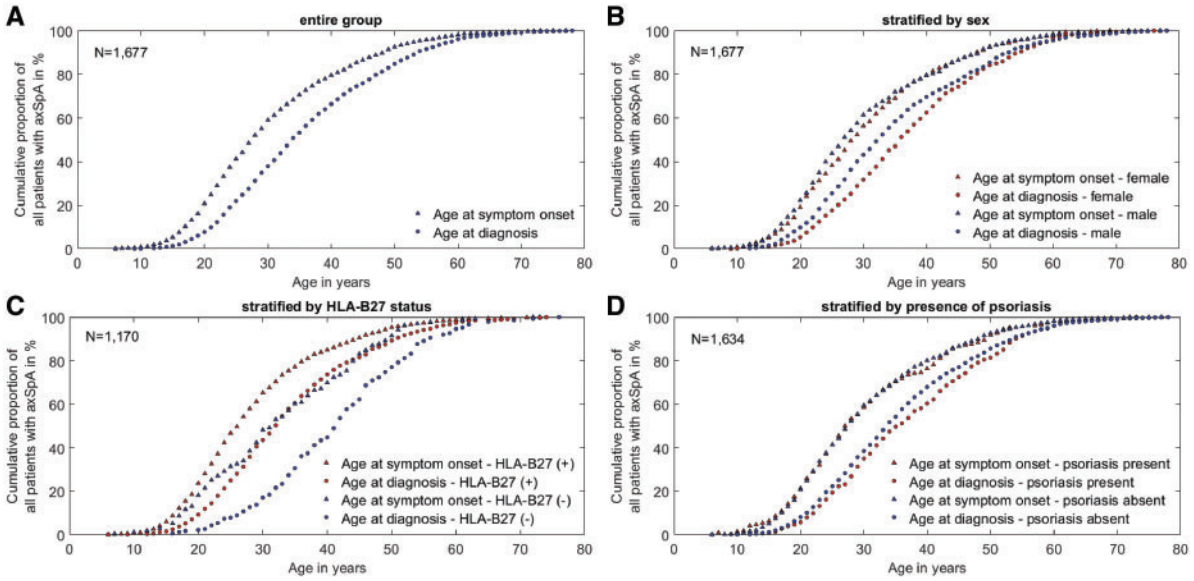
Patients in the highest tertile of diagnostic delay ($\geqslant$4.9 years) were more often female, less often carried the HLA-B27 gene, presented more often with psoriasis and were on average 5 years younger at symptom onset compared with patients in the lowest tertile of diagnostic delay ($<$0.7 years; Supplementary Table S1, available at *Rheumatology* online). Further, patients in the highest tertile of diagnostic delay more often had a medium or high level of education compared with those in the lowest tertile of diagnostic delay. Similar results were obtained when patients were grouped according to the median diagnostic delay (Supplementary Table S1, available at *Rheumatology* online).

Fig. 1 shows the cumulative distribution of age at symptom onset and age at diagnosis in axSpA in the entire group and in subgroups stratified by sex, HLA-B27 status and presence of psoriasis. As expected, the vast majority ($\sim$90%) of the patients were $<$45 years of age at the time of symptom (back pain) onset.

Overall, 407 patients were diagnosed between 1996 and 2005 and 484 patients between 2006 and 2015. The diagnostic delay was not substantially different in either period: for patients diagnosed between 1996 and 2005 the mean diagnostic delay was 6.3 years (median 2.6) and for patients diagnosed between 2006 and 2015 the mean diagnostic delay was 7.4 years (median 2.7).

Univariable linear regression showed that younger age at symptom onset, female sex, a negative HLA-B27 status and the presence of psoriasis were associated with a

Fig. 1 Cumulative distribution of age at symptom onset and age at diagnosis in patients with axSpA



longer diagnostic delay (Table 1). Stepwise multivariable linear regression analysis confirmed the significant association of the mentioned factors with a diagnostic delay while controlling for other variables (Table 1).

Discussion

The objective of this nationwide population-based study conducted in Germany was to assess the current diagnostic delay in axSpA and to determine the factors associated with it. We found a mean diagnostic delay (the time between back pain onset and diagnosis) of 5.7 years and a median diagnostic delay of 2.3 years if all 1677 patients were analysed. Surprisingly, we observed no decrease of the diagnostic delay in the period 2006–2015 as compared with the period 1996–2005: the mean diagnostic delay was 7.4 years (median 2.7) and 6.3 (2.6), respectively. These data indicate that despite all recent developments related to the concept, diagnosis and treatment of axSpA, we still face the problem of a delayed diagnosis. Even in the last few years, in about half of the patients it took >2.5 years to get the right diagnosis. It is possible, however, that more time is needed in order to observe an improvement of the diagnostic delay related to the focus on early diagnosis triggered by the introduction of the Assessment of Spondyloarthritis International Society (ASAS) classification criteria for axSpA in 2009. Our data are consistent with the results of a recent study based on routinely recorded clinical data on axSpA patients attending two large UK secondary care centres indicating a stable mean diagnostic delay of 8–9 years and a median delay of 5 years prior to and after 2009 (the year of publication of the ASAS classification criteria for axSpA) [10].

In the analysis of factors associated with diagnostic delay, we found that HLA-B27 negativity, female sex, younger age at symptom onset and the presence of psoriasis were factors independently associated with a longer diagnostic delay in patients with axSpA. Two of these factors, HLA-B27 negativity [11] and female sex [12], have been reported previously and are rather easy to explain. HLA-B27 is often used by primary care physicians in Germany as a screening/referral parameter for axSpA, and for rheumatologists it is one of the most important diagnostic tests. Thus being HLA-B27 negative decreases both the probability of being referred to a rheumatologist and the probability of being diagnosed with axSpA. Similar reasoning is also true for female sex: radiographic axSpA/AS has been repeatedly described in the past as a disease affecting predominantly males, but recent data show that at the non-radiographic disease stage, females are even more prevalent [13–15]. Thus being female obviously decreases the chance to be referred to a rheumatologist with a suspicion of axSpA. Also, a milder disease course in females with less structural damage in the axial skeleton [2, 16] might be a reason for a delayed diagnosis.

The impact of psoriasis on diagnostic delay indicates, in our view, a lack of established referral processes on the level of dermatologists related to axial manifestations of psoriatic disease/PsA. It seems that back pain in patients with psoriasis tends to be attributed to other reasons, despite the fact that up to one-third of patients with PsA have axial involvement [17].

The fourth independent factor associated with diagnostic delay is younger age at symptom onset. At first glance, this association seems counterintuitive since axSpA in the vast majority of cases starts between 20 and 40 years of age. However, in early adulthood the presence of back

Table 1 Factors associated with diagnostic delay in axSpA: results from univariable and multivariable linear regression analyses

Factors	Reference	Univariable analysis β (95% CI)	Multivariable analysis β (95% CI)
Sex, female	Male	1.62 (0.90, 2.33)	1.85 (1.06, 2.65)
Age at symptom onset	Per 10 years	−1.56 (−1.83, −1.28)	−1.91 (−2.29, −1.53)
HLA-B27 status, positive	Negative	−3.14 (−4.80, −1.49)	−3.61 (−5.14, −2.07)
Psoriasis, present	Not present	1.41 (0.24, 2.57)	1.40 (0.08, 2.73)
IBD, present	Not present	0.00 (−1.33, 1.34)	–
Uveitis, present	Not present	−0.01 (−0.79, 0.76)	–
Education level, low	Medium	−0.35 (−1.22, 0.52)	–
Education level, high	Medium	−0.37 (−1.24, 0.49)	–

pain may be explained by functional reasons [18], resulting in a delay of appropriate diagnostic tests for axSpA.

Our study has strengths and limitations. The large nationwide sample of patients with axSpA is an important strength of the study. Questionnaire data obtained from these patients contained valuable information on disease-related factors not available in insurance claims data.

Left censoring represents a potential limitation: in the present study, patients diagnosed in former decades with a long delay to diagnosis would have become too old to be included or are no longer alive. This might explain why the diagnostic delay in the two recent decades, which were analysed separately, was slightly higher compared with the entire population studied. However, when comparing the diagnostic delay in the two recent decades based on a sample stratified by age, the error due to left censoring is likely not very relevant. Recall bias is another potential limitation: patients with longer disease duration may have difficulty remembering the correct date of their first symptoms. However, a previous study concluded that the majority of patients with AS remembered the age at symptom onset with an inaccuracy of at most 1 year [19]. Further, the study was conducted in Germany, meaning that our results may not be applicable to countries with different health care systems and/or different referral practices. However, recent data from the UK [10] and data from a large multinational study [20] indicate a similar large diagnostic delay in the majority of countries across the globe. For the selection of patients we used the ICD-10 code M45 in order to identify subjects with axSpA. It is possible, however, that patients with early (i.e. non-radiographic) axSpA were recorded differently (for instance, M46) and were therefore not captured by the selection procedure. However, from 2014, the term nr-axSpA is incorporated in the M45 category of the ICD-10-GM.

In conclusion, the large diagnostic delay in axSpA remains one of the major challenges in modern rheumatology. Female sex, negative HLA-B27 status, the presence of psoriasis and younger age at symptom onset were factors associated with an increased diagnostic delay in the studied population. Specific referral strategies might be necessary in order to decrease the diagnostic delay in patients presenting with these characteristics.

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Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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2.2. Kriterien entzündlichen Rückenschmerzes bei der Diagnose einer axialen Spondyloarthritis

Damit die Diagnoseverzögerung bei axSpA kürzer wird ist es wichtig, dass Personen mit entsprechenden Symptomen für entzündlichen Rückenschmerz frühzeitig auch in der hausärztlichen Versorgung erkannt werden. Um schnell und einfach bestimmten zu können, bei wem Symptome zeitnah fachärztlich abgeklärt werden sollten, können verschiedene Diagnosekriterien genutzt werden. Die folgende Arbeit untersucht den diagnostischen Nutzen des entzündlichen Rückenschmerzes für die axSpA und vergleicht dabei die diagnostische Güte verschiedener Kriterien für entzündlichen Rückenschmerz.

Der nachfolgende Text entspricht dem Abstrakt der Arbeit:

> Poddubnyy D, Callhoff J, Spiller I, Listing J, Braun J, Sieper J, et al. Diagnostic accuracy of inflammatory back pain for axial spondyloarthritis in rheumatological care. RMD Open. 2018;4(2):e000825.
> https://doi.org/10.1136/rmdopen-2018-000825

Abstract

Objective Inflammatory back pain (IBP), the key symptom of axial spondyloarthritis (axSpA), including ankylosing spondylitis, has been proposed as a screening test for patients presenting with chronic back pain in primary care. The diagnostic accuracy of IBP in the rheumatology setting is unknown. **Methods** Six rheumatology centres, representing secondary and tertiary rheumatology care, included routinely referred patients with consecutive chronic back pain with suspicion of axSpA. IBP (diagnostic test) was assessed in each centre by an independent (blinded) rheumatologist; a second (unblinded) rheumatologist made the diagnosis (axSpA or no-axSpA), which served as reference standard. **Results** Of 461 routinely referred patients, 403 received a final diagnosis. IBP was present in 67.3%,

and 44.6% (180/403) were diagnosed as axSpA. The sensitivity of IBP according to various definitions (global judgement, Calin, Berlin, Assessment of SpondyloArthritis international Society criteria for IBP) was 74.4%–81.1 % and comparable to published figures, whereas the specificity was unexpectedly low (25.1%–43.9%). The resulting positive likelihood ratios (LR+) were 1.1–1.4 and without major differences between sets of IBP criteria. The presence of IBP according to various definitions increased the probability of axSpA by 2.5%–8.4% only (from 44.6% to 47.1%–53.0%). **Conclusions** The diagnostic utility of IBP in the rheumatology setting was smaller than expected. However, this was counterbalanced by a high prevalence of IBP among referred patients, demonstrating the effective usage of IBP in primary care as selection parameter for referral to rheumatology. Notably, this study illustrates potential shifts in specificity and LR+ of diagnostic tests if these tests are used to select patients for referral.

RMD Open
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ORIGINAL ARTICLE

Diagnostic accuracy of inflammatory back pain for axial spondyloarthritis in rheumatological care

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ABSTRACT

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Methods Six rheumatology centres, representing secondary and tertiary rheumatology care, included routinely referred patients with consecutive chronic back pain with suspicion of axSpA. IBP (diagnostic test) was assessed in each centre by an independent (blinded) rheumatologist; a second (unblinded) rheumatologist made the diagnosis (axSpA or no-axSpA), which served as reference standard.

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Conclusions The diagnostic utility of IBP in the rheumatology setting was smaller than expected. However, this was counterbalanced by a high prevalence of IBP among referred patients, demonstrating the effective usage of IBP in primary care as selection parameter for referral to rheumatology. Notably, this study illustrates potential shifts in specificity and LR+ of diagnostic tests if these tests are used to select patients for referral.

Key messages

What is already known about this subject?

- Inflammatory back pain (IBP), the key symptom in axial SpA, is used for diagnostic purposes.
- Despite, its diagnostic accuracy in the rheumatology setting according to high level standards (e.g. STARD, Standards for Reporting of Diagnostic Accuracy) is unknown.

What does this study add?

- In the rheumatology setting IBP was a common finding among referred patients suggesting the effective use of IBP as selection parameter for referral in primary care.
- As a result, the specificity of IBP was lower and the diagnostic gain of IBP was smaller than expected.
- In the rheumatology setting no striking differences among defined IBP criteria (Calin, Berlin, ASAS) were found, yet the Calin criteria were least specific.

How might this impact on clinical practice?

- The study shows global judgement on the presence or absence of IBP as done in routine rheumatological care is influenced by knowledge of other SpA features.
- Rheumatologists should realize that diagnostic test characteristics such as specificity and likelihood ratios vary if the diagnostic test is used as selection parameter in primary care.

INTRODUCTION

Inflammatory back pain (IBP) is the key clinical symptom of axial spondyloarthritis (axSpA), including non-radiographic axSpA (nr-axSpA) and ankylosing spondylitis (AS, r-axSpA), and is often present at disease onset. IBP describes a spectrum of symptoms including (1) insidious onset of back pain, (2) morning stiffness in the lower back, (3) improvement of back pain with exercise, (4) no improvement with rest, (5) awakening at night or early morning because of back pain and (6) alternating buttock pain. Defined sets of IBP criteria are the Calin criteria,[1] Berlin criteria[2] and the Assessment of SpondyloArthritis international Society (ASAS) IBP experts criteria[3]; the latter was applied in the ASAS classification criteria for axSpA study.[4 5] The published sensitivities (70.1%–95%) and specificities (72.5%–81.3%%) for various sets of IBP criteria reveal calculated

positive likelihood ratios (LR+), a measure of diagnostic utility, of 2.9–3.9. Accordingly, a LR+ of 3–4 for IBP has been proposed as best estimate for diagnostic purposes in daily practice.[6] Assuming a background prevalence of 5% of axSpA among patients with chronic back pain in primary care, it has further been estimated that the presence of IBP increases the likelihood of axSpA by 9%–11% (from 5% to 14%–16%).[6] IBP has also been proposed[7] and has been proven effective as a parameter for selecting patients with chronic back pain in primary care for referral to rheumatology.[7–13] No diagnostic accuracy study on IBP in the rheumatology setting is available to date.

METHODS

Study centres

The Diagnostic Accuracy of Inflammatory Back pain study (DIVERS) was designed according to recommendations in the field of diagnostic studies including the Standards for Reporting of Diagnostic Accuracy recommendations.[14 15] DIVERS was conducted in six rheumatology centres across Germany: four general rheumatology practices (secondary care) distributed across the country, one large hospital for rheumatic diseases and one university hospital (tertiary care).

Patients

Eligible patients were routinely referred to rheumatology, had to have chronic back pain of ≥3 months and age at onset of ≤45 years and no clear diagnosis. Patients with a known diagnosis of axSpA were excluded. To avoid selection bias, participating centres were strongly encouraged to include consecutively all newly referred patients with chronic back pain with suspicion of axSpA. No specific referral strategies were set up for this study.

Study procedures

In each centre, two rheumatologists were involved: R-care and R-blind. R-care took routine care of the patient, ordered diagnostic tests as needed and made the final diagnosis of axSpA or no-axSpA. In contrast, R-blind took the clinical history regarding IBP features only, but was blinded to all other disease features otherwise. Both R-care and R-blind documented their findings independently of each on a prespecified case report form. The clinical diagnosis (axSpA or non-SpA) made by R-care served as reference standard. Since the study was conducted in routine rheumatology care, the sequence of consultation by either R-care or R-blind was left to the discretion of the participating centres and was driven primarily by feasibility aspects (R-care first 76%, R-blind first 24%).

In addition, patients were asked to complete a short self-reported questionnaire on IBP features in the rheumatologist's waiting room prior to the consultation, with answering modalities of 'yes' or 'no' to each IBP question.

The time period between first presentation to the rheumatology centre including the assessment of IBP by R-blind and final diagnosis (axSpA or no-axSpA) was in the range of 2–8 weeks. The first patient was included in March 2009 and the last patient in June 2010.

Study end points and data analysis

The diagnostic test of interest (presence/absence of IBP) was assessed by R-blind according to four definitions: (1) IBP by global judgement by the rheumatologist (ie, judgement on IBP independent of formal IBP criteria; yes/no), (2) Calin criteria, (3) Berlin criteria and (4) ASAS criteria for IBP. The global judgement (yes/no) on IBP was further categorised into 'uncertain', 'moderately confident', 'confident' and 'very confident'. Sensitivity, specificity, positive and negative LRs (LR+ and LR−), positive and negative predictive values (PPV and NPV) with corresponding 95% CI of IBP and the net increase (%) in disease probability of axSpA were calculated. The agreement on the presence of IBP between R-blind and R-care was assessed by percentage agreement and Cohen's kappa; the latter interpreted according to the method of Landis and Koch.[16]

RESULTS

Of 476 eligible patients, 13 patients did not fulfil the inclusion criteria and were excluded. R-blind decided on the presence/absence of IBP in 461/463 patients. IBP by global judgement (R-blind) was present in 306/461 patients (66.4%). The level of confidence on IBP by R-blind in these 461 patients was as following: 'very confident' in 17.1% of patients, 'confident' in 62.5%, 'moderately confident' in 18.9% and 'uncertain' in 1.5%. The final clinical diagnosis by R-care (reference standard) was missing in four and considered uncertain in 54 patients. Thus, 403 patients with an assessment of IBP by R-blind (67.3% had IBP) and a definite diagnosis by R-care (180 with definite axSpA—88 with AS, 92 with nr-axSpA—and 223 with no-axSpA) were included in the final analysis (patient flow chart shown in figure 1). The clinical characteristics of the patients are presented in table 1. The prevalence of IBP was generally higher in patients with axSpA (with no difference between AS and nr-axSpA) as compared with patients without axSpA (table 2).

The formal agreement on the global judgement on the presence of IBP between R-blind and R-care was moderate (kappa 0.45; 95% CI 0.36 to 0.54) with percentage agreement 74.9%. Similar rates of agreement between R-blind and R-care were obtained for the various defined IBP criteria: kappa 0.43 (95% CI 0.32 to 0.53; percentage agreement 80.2%) for the Calin criteria; kappa 0.52 (95% CI 0.43 to 0.61; percentage agreement 80.0%) for Berlin criteria and kappa 0.46

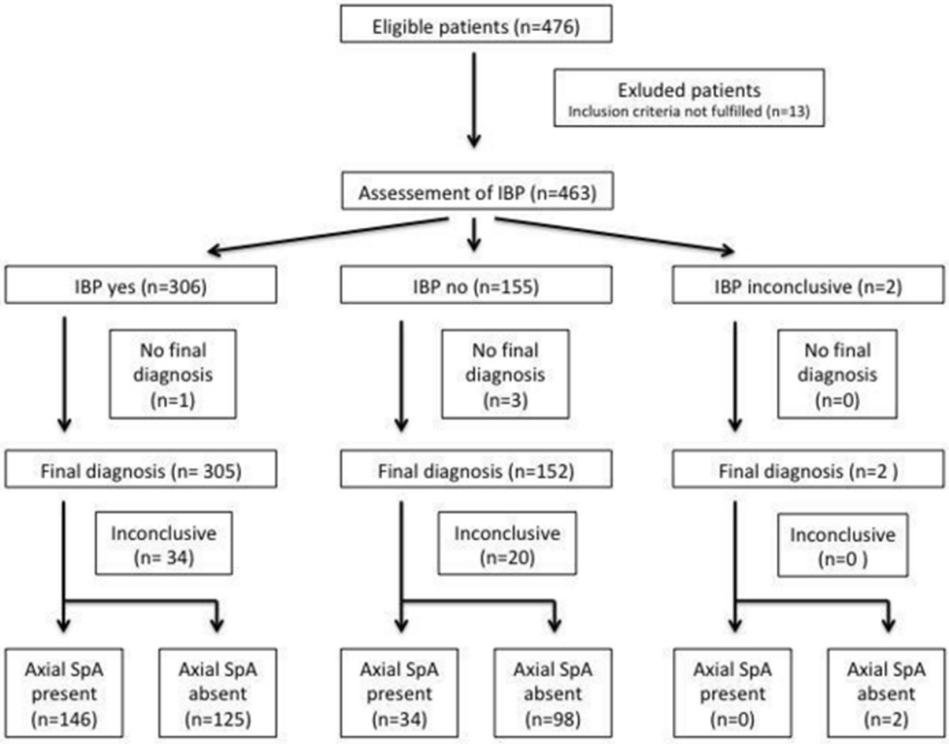

Figure 1 Flow chart of patients with chronic back pain included in diagnostic accuracy of inflammatory back pain study. IBP, inflammatory back pain; SpA, spondyloarthritis.

Table 1 Clinical, laboratory and imaging characteristics of patients with chronic back pain who had judgement on IBP and who received a final diagnosis

	AxSpA			
Parameter	**AS (n=88)**	**Nr-axSpA (n=92)**	**No-axSpA (n=223)**	**All (n=403)**
Age, years (mean±SD)	36.1±10.2	32.8±9.3	42.7±11.3	39.0±11.4
Male sex, n (%)	60 (68.2)	54 (58.7)	79 (35.4)	193 (47.9)
HLA-B27 positive, n (%)	79 (89.8)	70 (76.1)	83 (37.2)	232 (57.6)
Back pain duration, years (mean±SD)	9.0±7.8	5.3±6.9	12.5±10.9	10.1±9.9
Peripheral oligoarthritis, n (%)	12 (13.6)	20 (21.7)	32 (14.3)	64 (15.9)
Enthesitis, n (%)	21 (23.9)	16 (17.4)	33 (14.8)	71 (17.6)
Dactylitis, n (%)	2 (2.3)	5 (5.4)	10 (4.5)	17 (4.2)
Uveitis, n (%)	13 (14.8)	18 (19.6)	11 (4.9)	42 (10.4)
History of IBD, n (%)	2 (2.3)	4 (4.4)	0 (0)	6 (1.5)
Psoriasis, n (%)	2 (2.3)	13 (14.1)	16 (7.2)	31 (7.7)
SpA family history, n (%)	17 (19.3)	24 (26.1)	45 (20.1)	86 (21.3)
CRP, mg/L (mean±SD)	11.0±16.4	7.1±9.2	2.9±4.3	5.7±9.9
ESR, mm/hour (mean±SD)	22.7±20.8	15.2±13.3	12.0±10.3	15.2±14.6
Radiographic sacroiliitis according to the mNY criteria, n/N (%)	78/85 (91.8)	0/85	0/208	85/378 (22.5)
Active inflammatory changes in the SIJ on MRI, n/N (%)	37/48 (77.1)	51/70 (72.9)	2/77 (2.6)	90/195 (46.2)
Chronic inflammatory changes in the SIJ on MRI, n/N (%)	32/48 (66.7)	38/70 (54.3)	0/77 (0)	70/195 (35.9)
Active inflammatory changes in the spine on MRI, n/N (%)	15/36 (41.7)	13/35 (37.1)	5/84 (6.0)	33/155 (21.3)
Chronic inflammatory changes in the spine on MRI, n/N (%)	11/36 (30.6)	3/35 (8.6)	3/84 (3.6)	17/15 (11.0)

AS, ankylosing spondylitis; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HLA, human leucocyte antigen; IBD, inflammatory bowel disease; MRI, MRI resonance imaging; SIJ, sacroiliac joint; SpA, spondyloarthritis; mNY criteria, modified New York criteria; nr-axSpA, non-radiographic axial spondyloarthritis.

Table 2 The prevalence of IBP (%) according to different criteria in patients referred because of chronic back pain

Assessor	IBP according to…	AxSpA		No-axSpA (n=223)	All (n=403)
		AS (n=88)	nr-axSpA (n=92)		
Blinded rheumatologist	Global evaluation	80.7	81.5	56.1	67.3
	Calin's criteria	79.6	79.4	74.9	76.9
	Berlin Criteria	81.8	80.4	67.7	73.7
	ASAS criteria	75.0	73.9	60.5	66.8
Diagnosing rheumatologist	Global evaluation	92.1	88.0	41.3	63.0
	Calin's criteria	87.5	82.6	73.1	78.4
	Berlin criteria	85.2	82.6	55.2	68.0
	ASAS criteria	89.8	78.3	64.6	73.2
Patient	Calin's criteria	73.6	76.7	79.5	77.5
	Berlin criteria	87.4	85.6	81.7	83.8
	ASAS criteria	79.3	68.9	69.0	71.2

AS, ankylosing spondylitis; ASAS, Assessment of SpondyloArthritis international Society; IBP, inflammatory back pain; SpA, spondyloarthritis; nr-axSpA, non-radiographic axial spondyloarthritis.

(95% CI 0.37, 0.56; percentage agreement 77.3%) for the ASAS criteria.

Diagnostic accuracy of IBP

For diagnostic accuracy analyses of IBP, data from AS and nr-axSpA were pooled (table 3). IBP by R-blind had a sensitivity of 74%–81% and a specificity of 25%–44% for the diagnosis of axSpA, depending on the IBP definition applied. Interestingly, global judgement on IBP by R-blind numerically exceeded the three sets of defined IBP criteria in terms of sensitivity and specificity; yet, the resulting positive LRs overall were low, ranging from 1.1 (Calin criteria) to 1.4 (global judgement of IBP) (table 3). The results were similar when we stratified for single study sites or for type of centre: for example, the LR+ for IBP according to ASAS criteria by R-blind was 1.3 (hospital based) and 1.1 (private

Table 3 Sensitivity, specificity, PPV and NPV of IBP for the diagnosis of axSpA

Assessor	IBP according to…	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV (95% CI)	NPV (95% CI)	LR+ (95% CI)	LR– (95% CI)
Blinded rheumatologist	Global evaluation	81.1 (75.4 to 86.8)	43.9 (37.3 to 50.7)	53.9 (48.0 to 59.8)	74.2 (66.8 to 81.7)	1.4 (1.3 to 1.7)	0.4 (0.3 to 0.6)
	Calin's criteria	79.4 (73.5 to 85.4)	25.1 (19.6 to 31.3)	46.1 (40.6 to 51.9)	60.2 (50.0 to 70.2)	1.1 (1.0 to 1.2)	0.8 (0.6 to 1.2)
	Berlin criteria	81.1 (75.4 to 86.8)	32.3 (26.2 to 38.6)	49.2 (43.3 to 55.0)	67.9 (58.7 to 76.7)	1.2 (1.1 to 1.3)	0.6 (0.4 to 0.8)
	ASAS criteria	74.4 (68.1 to 80.8)	39.5 (33.0 to 46.1)	49.8 (43.8 to 55.8)	65.7 (57.3 to 73.4)	1.2 (1.1 to 1.4)	0.6 (0.5 to 0.9)
Diagnosing rheumatologist	Global evaluation	90.0 (85.6 to 94.4)	58.7 (52.1 to 65.2)	63.8 (57.8 to 69.7)	87.9 (81.9 to 92.7)	2.2 (1.9 to 2.6)	0.2 (0.1 to 0.3)
	Calin's criteria	85.0 (79.8 to 90.2)	26.9 (21.4 to 33.0)	48.4 (42.8 to 54.1)	69.0 (58.4 to 78.2)	1.2 (1.1 to 1.3)	0.6 (0.4 to 0.8)
	Berlin criteria	83.9 (78.5 to 89.3)	44.8 (38.2 to 51.6)	55.1 (49.0 to 61.1)	77.5 (69.7 to 84.4)	1.5 (1.3 to 1.7)	0.4 (0.2 to 0.5)
	ASAS criteria	83.9 (78.5 to 89.3)	35.4 (29.2 to 41.8)	51.2 (45.3 to 57.0)	73.2 (64.2 to 80.8)	1.3 (1.2 to 1.5)	0.5 (0.3 to 0.7)
Patient	Calin's criteria	75.1 (68.8 to 81.5)	20.6 (15.6 to 26.3)	43.3 (37.7 to 49.0)	50.6 (39.8 to 61.0)	0.9 (0.8 to 1.1)	1.2 (0.8 to 1.7)
	Berlin criteria	86.4 (81.4 to 91.5)	18.3 (13.5 to 23.7)	46.1 (40.6 to 51.6)	62.5 (50.0 to 74.0)	1.1 (1.0 to 1.2)	0.7 (0.5 to 1.2)
	ASAS criteria	74.0 (67.6 to 80.5)	31.1 (25.0 to 37.6)	46.5 (40.5 to 52.4)	59.7 (50.5 to 68.7)	1.1 (0.9 to 1.2)	0.8 (0.6 to 1.1)

ASAS, Assessment of SpondyloArthritis international Society; IBP, inflammatory back pain; LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; SpA, spondyloarthritis; axSpA, axial spondyloarthritis.

practices), respectively. Overall, the LR+ as a measure of diagnostic utility of the symptom of IBP for the diagnosis of axSpA was small and substantially smaller than expected from published data (LR+ 3–4) due to low specificity, independently of the definition of IBP being applied.

The ASAS defined IBP criteria had the lowest sensitivity (74.4%), while the Berlin criteria and global judgement of IBP had the highest sensitivity (both 81.1%). The specificity of IBP according to R-blind varied from 24.9% (Calin criteria) to 43.9% (global judgement) (table 3). There were no striking differences between the three sets of IBP criteria with regard to PPV and NPV: the Calin criteria performed slightly less well than the Berlin and ASAS criteria.

In the original publication of the Berlin criteria, it was speculated that the presence of ≥3 out of 4 items (instead of ≥2 out of 4) would yield a high diagnostic gain (estimated LR+ 12.4; specificity 97.3%, sensitivity 33.6%).[2] In the settings of DIVERS, however, the sensitivity and specificity of ≥3 out of 4 items of the Berlin criteria were 59.8% and 59.9%, respectively, and resulted in a small increase of the LR+ from 1.2 to 1.5 only.

Single IBP features

Analysing single IBP parameters, the highest sensitivity for the diagnosis of axSpA was observed for 'improvement of back pain with exercise' (88.9%), which, however, had a low specificity (22.7%) (table 4). 'Alternating buttock pain' had the lowest sensitivity (60.0%) but the highest specificity (58.2%), and the highest LR+ of 1.4 for a single IBP feature according to R-blind.

Blinded as compared to unblinded assessment of IBP

It can be assumed that the judgement on a diagnostic test like IBP, which is subject to interpretation, will be influenced by knowledge of other diagnostic test results ('diagnostic bias'). Indeed, both sensitivity 90.0% versus 81.1% and specificity 58.2% versus 44.0% of IBP according to global judgement were higher for R-care (unblinded) than for R-blind (table 3). This indeed demonstrates a moderate diagnostic bias of R-care in the assessment of IBP by knowledge of other SpA features. In contrast, the comparison between R-blind and R-care according to formal sets of IBP criteria (Calin, Berlin, ASAS) revealed no consistent differences in specificity but lower sensitivities for all three sets of criteria when assessed by R-blind (table 3). This suggests that 'global judgement' on IBP is more susceptible to diagnostic bias than defined sets of IBP criteria.

IBP self-assessment by the patient

With regard to fulfilment of defined sets of IBP criteria, little differences were found in the self-assessed prevalence of IBP between patients with axSpA and patients without axSpA (table 2): the specificities of defined IBP criteria, and of single IBP features, were even lower if self-assessed by the patient, while the sensitivities were comparable to those as assessed by R-blind (tables 3 and 4), resulting in even slightly lower LR+ of between 0.9 and 1.1 overall.

Diagnostic gain of IBP for the diagnosis of axSpA

In DIVERS, axSpA was diagnosed in 44.6% (pretest probability of axSpA). According to global judgement on IBP by R-blind, the presence of IBP (LR+ 1.4) resulted in a post-test probability of axSpA of 53%. Thus, a moderate diagnostic gain of IBP of 8.4% remained despite the low LR+. For comparison, the presence of IBP according to R-care—unblinded to other patient findings including human leucocyte antigen (HLA)-B27 and imaging, and therefore somewhat biassed—had resulted in an increase of axSpA by as much as 19.5% (from 44.6% to 63.9%).

Table 4 Sensitivity and specificity of single IBP parameters as assessed by the diagnosing rheumatologist, the blinded rheumatologist and patient for the diagnosis of axSpA

	Blinded rheumatologist			Diagnosing rheumatologist			Patient		
IBP parameter	Sensitivity, % (95% CI)	Specificity, % (95% CI)	LR+	Sensitivity, % (95% CI)	Specificity, % (95% CI)	LR+	Sensitivity, % (95% CI)	Specificity, % (95% CI)	LR+
Insidious onset	75.6 (69.3 to 81.8)	24.4 (18.8 to 30.1)	1.0	83.9 (78.5 to 89.3)	19.6 (14.4 to 24.7)	1.0	76.2 (69.8 to 82.5)	15.3 (10.5 to 20.1)	0.9
Morning stiffness ≥30 min	71.1 (63.8 to 78.3)	33.9 (27.0 to 40.8)	1.1	67.4 (59.8 to 74.9)	37.7 (30.4 to 45.1)	1.1	69.4 (62.5 to 76.3)	30.1 (24.0 to 36.2)	1.0
Improvement with exercise	88.9 (84.3 to 93.5)	22.7 (17.2 to 28.1)	1.2	85.6 (80.4 to 90.7)	30.7 (24.6 to 36.7)	1.2	83.0 (77.4 to 88.7)	18.6 (13.4 to 23.8)	1.0
No improvement with rest	73.9 (67.5 to 80.3)	44.9 (38.4 to 51.4)	1.3	81.6 (75.9 to 87.2)	41.8 (35.3 to 48.2)	1.4	81.1 (75.1 to 87.1)	30.8 (24.5 to 37.0)	1.2
Pain at night	74.4 (68.1 to 80.8)	33.8 (27.6 to 40.0)	1.1	82.8 (77.3 to 88.3)	30.1 (24.8 to 36.9)	1.2	77.6 (71.4 to 83.8)	26.9 (21.1 to 32.8)	1.1
Alternating buttock pain	60.0 (52.8 to 67.2)	58.2 (51.8 to 64.7)	1.4	57.8 (50.6 to 65.0)	63.4 (57.0 to 69.7)	1.6	68.2 (61.3 to 75.1)	43.4 (36.8 to 50.0)	1.2

IBP, inflammatory back pain; LR, likelihood ratio; SpA, spondyloarthritis; axSpA, axial spondyloarthritis.

DISCUSSION

DIVERS is the first real-life diagnostic accuracy study on IBP as a diagnostic test for axSpA in the rheumatology setting, that is, in secondary and tertiary care. We found a net diagnostic gain of only 2.5%–8.4%, if IBP is present, for the likelihood of a diagnosis of axSpA. Thus, one important finding at first glance is that IBP in the rheumatology setting contributes little to establishing the diagnosis of axSpA. On the other hand, the majority of referred patients had IBP, suggesting an effective selection in primary care of patients presenting with chronic back pain for referral to rheumatology. Moreover, our study shows that in the rheumatology setting, none of the defined sets of IBP criteria (Calin, Berlin, ASAS) clearly outperformed another one; yet, a tendency for the Calin criteria being the least specific set was found.

The sensitivity of IBP according to various defined IBP criteria (74.4%–81.1%) or to global judgement on IBP (81.1%) among patients with axSpA in DIVERS was very similar to published figures of 70.1%–95% in patients with AS/axSpA.[1–3] However, we found substantially lower specificities for all defined sets of IBP criteria, ranging from 25.2% to 39.5%, as compared with the original publications on IBP (72.5%–81.3%).[1–3] As a result, the calculated LR+ were low (1.1–1.2) as compared with published LR+ for these IBP definitions of 2.9–3.9.[1–3] A plausible explanation for the differences in the specificities of IBP criteria could be the fact that in two of the three earlier studies,[1 2] well-selected patients with either a clear diagnosis of axSpA or of mechanical back pain (no-axSpA) were included (convenience sample), whereas in our study undiagnosed and newly referred patients were included, thereby reflecting better daily rheumatology practice. Since the prevalence of IBP was high among referred patients, one must assume that IBP has operated as a selection parameter in primary care that had triggered referral to the rheumatologist. This unmeasured channelling process led to a population of referred patients with chronic back pain who were enriched for the presence of IBP. In fact, it has been proposed in 2005, and has subsequently proven effective, to select in primary care for referral to rheumatology chronic back patients with age at onset ≤45 years and at least one additional SpA feature such as IBP or a positive HLA-B27 test, both of which increase the likelihood of having axSpA.[13] In epidemiological studies on unselected back pain, prevalence figures for IBP of 5%–15% for acute and of 28%–35% for chronic back pain have been reported.[17 18] The high prevalence of IBP of 67.3% in our study indeed supports the notion that IBP had been used by primary care physicians to select patients for referral, although this was not specifically intended.

The selection of patients with certain SpA features for referral is also illustrated in our study by the high prevalence of other SpA features including HLA-B27 (57.6%), a positive family history for SpA (21.3%) or uveitis (10.4%); all of them leading to enrichment of patients with a higher likelihood of having axSpA. In fact, the selected referral of patients with back pain more likely to have axSpA is eventually reflected by the high rate of a final diagnosis of axSpA (44.6%) in DIVERS which is much higher than reported prevalences of axSpA of around 5%–12% in unselected patients with chronic back pain.[19 20] Interestingly, studies with a study design similar to DIVERS also revealed high prevalence rates of axSpA among referred patients: in the international ASAS classification criteria for axSpA study, the prevalence of axSpA was 66%,[5] and in the SPondyloArthritis Caught Early cohort, axSpA was diagnosed in 41%.[21] Although no structured referral protocol was recommended in either of these studies, an unmeasured preselection process had undoubtfully taken place in both,[22] suggesting 'unmeasured' selection of patients for referral likely occurring in other countries and settings as well.

The low LR+ of 1.1–1.2 for defined sets of IBP criteria suggests at first glance a minor, if any, diagnostic utility of IBP in the rheumatology setting. It seems that the diagnostic utility of IBP has been already 'used up' at the time when the patient is referred to the rheumatologist. Yet, a small diagnostic gain is indeed retained, partially because the pretest probability (prevalence of axSpA) was substantially higher in the rheumatology setting than in primary care: the presence of IBP according to global judgement by the blinded assessor (LR+ 1.4) resulted in an increase of the probability of axSpA from 44.6% to 53%, implicating a net diagnostic gain of 8.4%, whereas the increase with fulfilment of Calin criteria (2.4%), Berlin (4.5%) and ASAS criteria (4.5%) was lower than the estimated net diagnostic gain of 9%–11% for IBP among unselected patients with chronic back pain in primary care (probability of axSpA increases in primary care from 5% to 14%–16%).[6 19 23]

In DIVERS, we also analysed single IBP features, among which 'alternating buttock pain' had the highest specificity and the highest LR+ of 1.4, followed by 'no improvement with rest' (LR+ 1.3), suggesting that these items may provide some diagnostic information in the rheumatology setting. We also addressed the self-assessment of IBP by the patient. The resulting sensitivities were comparable to those by the blinded rheumatologist. However, the specificities were similar or even lower. The specificity of self-assessment of IBP symptoms in unselected patients in primary care is expected to be higher but cannot be properly addressed in our study.[7 13 24]

The knowledge of SpA features other than IBP that drive towards or away from a diagnosis of axSpA is likely to influence the global judgement on the presence or absence of IBP. Indeed, this potential bias is illustrated by both a higher sensitivity and higher specificity (with a resulting higher LR+ of 2.2 vs 1.4) for the diagnosing (unblinded) as compared with the blinded

rheumatologist in DIVERS and underscores the necessity in diagnostic accuracy studies for a diagnostic test like IBP, which is subject to interpretation, to be assessed in a blinded fashion.[14 15]

The strengths of our study are the high standards for the conduct and reporting of diagnostic studies including the prospective study design, the independent assessment of the diagnostic test of interest (IBP) without knowledge of other test results,[14 15] the multicentre study design with secondary care (four private practices) as well as tertiary care centres (one university hospital and one large community hospital specialised in rheumatology) and the large number of consecutive patients. A potential weakness of our study conducted in routine rheumatology care is the fact that not all patients diagnosed as no-axSpA underwent MRI. However, only 22 of patients without MRI (9.8% of all patients without SpA patients) had a clinical context (IBP plus positive HLA-B27) strongly suggesting axSpA: if all of these patients had shown sacroiliitis on MRI and had been diagnosed axSpA, a scenario that is unlikely, the specificity of IBP (global judgement) had increased from 43.9% to 48.8% and the LR+from 1.4 to 1.56.

Of interest, our study strikingly shows how test characteristics and the resulting LR+ vary, depending on the setting (primary vs secondary/tertiary care) where these tests are applied and depending on whether parameters have operated already as selection parameters for referral. The understanding of these potential shifts in specificity and LR+ of diagnostic tests is of general importance when interpreting data from any study on diagnostic test characteristics in medicine. The results of this study also confirm that a diagnosis of axSpA cannot be made by the presence or absence of single parameters (in this case of IBP) but only by assessment of all available clinical, laboratory and imaging parameters, interpreted by an experienced physician and after careful exclusion of other diagnoses.[23]

In summary, rheumatologists must be aware that their global judgement on IBP might be influenced by knowledge of other SpA parameters. Rheumatologists must also be aware that many patients referred to them for a diagnostic workup of axSpA will have IBP because IBP effectively operates in primary care as a selection criterion for referral. Although the specificity of IBP (and the resulting LR+) is low in the rheumatology setting, a small diagnostic gain remains.

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2.3. Parodontitis bei Patienten mit rheumatoider Arthritis

Auch die Diagnose bestimmter Komorbiditäten spielt eine wichtige Rolle für die Behandlung entzündlich-rheumatischer Erkrankungen. Es gibt einige Studien die zeigen, dass Personen mit RA häufiger eine Parodontitis haben als Kontrollen aus der Normalbevölkerung(32). Erste Hinweise zeigen, dass sich eine Behandlung der Parodontitis positiv auf die Entzündungswerte gemessen an der Blutsenkungsgeschwindigkeit auswirkt(33).

Um den Zusammenhang von Parodontitis und RA weiter zu erforschen ist es wichtig, RA-Patient*innen mit Parodontitis zuverlässig identifizieren zu können. Nicht immer ist es bei epidemiologischen Studien möglich, alle Personen zahnärztlich untersuchen zu lassen. Die folgende Arbeit untersuchte daher den diagnostischen Nutzen eines patientenberichteten Fragebogens, um in einer RA-Population Personen mit Parodontitis identifizieren zu können.

Der nachfolgende Text entspricht dem Abstrakt der Arbeit:

> Callhoff J, Dietrich T, Chubrieva M, Klotsche J, Zink A. A patient-reported questionnaire developed in a German early arthritis cohort to assess periodontitis in patients with rheumatoid arthritis. Arthritis Res Ther. 2019;21(1):197
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Abstract

Background: The aim of this study was to develop a patient-reported questionnaire that is suitable to detect periodontitis (PD) in patients with rheumatoid arthritis (RA).

Methods: A self-reported questionnaire containing 12 items potentially relevant to PD and dentists' semiquantitative assessment of PD (no/mild/moderate/severe) was obtained from 353 patients from an early arthritis cohort. Available radiographs (n = 253) and blinded assessment of 3 independent dentists were used for validation. By defining the dentists' assessment as the reference standard,

relevant questionnaire items were identified with factor analysis methods. Receiver operator characteristic (ROC) plots were used to determine sensitivities and specificities to detect PD in varying severity. Ordinal regression models were used to determine the coefficients for the final score.

Results: Seventy percent had at least mild PD. The items from the questionnaire correlating best with the dentists' assessment were selected for a final 6-item score (number of teeth, gum pockets, receding gums, loose teeth, receding jaw bone and tooth extractions and age). For the detection of any/moderate/severe PD, the bias-corrected areas under the curve (AUC) were 0.81/0.83/0.90. Sensitivity to detect mild PD was 85% and specificity 57%. Very high specificity was achieved for the detection of severe PD with 99% at the cost of low sensitivity (28%).

Conclusions: This patient-reported six-item score has moderate diagnostic properties to study PD in RA patients in epidemiological settings. We propose to use the score as a measure of periodontitis without applying cut-off values.

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A patient-reported questionnaire developed in a German early arthritis cohort to assess periodontitis in patients with rheumatoid arthritis

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Abstract

Background: The aim of this study was to develop a patient-reported questionnaire that is suitable to detect periodontitis (PD) in patients with rheumatoid arthritis (RA).

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Conclusions: This patient-reported six-item score has moderate diagnostic properties to study PD in RA patients in epidemiological settings. We propose to use the score as a measure of periodontitis without applying cut-off values.

Keywords: Periodontitis, Rheumatoid arthritis, Self-reported questionnaire, Validation

Introduction

Over the past years, the association between chronic periodontitis (PD) and rheumatoid arthritis (RA) has received considerable attention [1–5]. In a systematic review of studies on the association of PD and RA [6], Kaur et al. reported good evidence for the association between PD and tooth loss and attachment loss in patients with RA. They also discuss several models for the "interplay between PD and RA", which include the possibilities that periodontitis precedes RA, that there are common underlying inflammatory pathways and that RA and PD exacerbate each other [6].

In a case-control study with 22 RA patients and 22 healthy controls, Wolff et al. confirmed evidence that patients with RA suffer from a higher risk of periodontal attachment loss [7]. Large epidemiological studies could help to gain further knowledge on the association of PD and parameters of disease activity in RA. However, it may not always be feasible to include the assessment of the periodontal status from trained study dentists in large epidemiological settings as was the case in the studies performed by Choi et al. [8] and Ayravainen et al. [3]. Therefore, a self-reported questionnaire would be helpful to assess PD in patients with RA. Several self-reported patient questionnaires have been developed in the past in

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various non-RA-specific populations with reasonable validity [9–12]. Coburn et al. [13] published a self-reported PD questionnaire that was evaluated in 617 patients with RA and osteoarthritis. This questionnaire included 6 questions on the periodontal status as well as sex, age, education and smoking behaviour and also showed moderate validity.

Taking into account the previous work by Dietrich et al. [11] and others [9, 10, 12], our aim was to develop a simple patient-reported questionnaire for PD that can be used for studying the relationship of RA and PD in epidemiological settings and to validate it in a large cohort of patients with RA.

Patients and methods

Early arthritis cohort

Patients from the early arthritis cohort study Course And Prognosis of Early Arthritis (CAPEA) were asked to participate in this project. CAPEA is a prospective, multicentre, non-interventional, observational study in which patients were enrolled between 2010 and 2013 [14]. Eligible patients had arthritis for less than 6 months. They were consecutively enrolled in rheumatology clinics and practices in Germany and observed for 2 years in order to investigate the prognostic value of early symptoms for the development of a chronic course of disease. Ethical approval for CAPEA was obtained from the Ethics Committee of the Charité University Medicine, Berlin, in May 2009 with an amendment for the periodontitis project in May 2012.

Patient-reported questionnaire on periodontitis

All patients enrolled in CAPEA until January 2013 were sent a questionnaire including 12 questions about their PD status and other items considering dental replacement, comorbidities, current medication and pain. The questionnaire items were as follows: “number of teeth” (0–28), “receding jaw bone” (0, no; 1, yes), “receding gums” (0, no; 1, at up to 3 teeth; 2, at 4 to 10 teeth; 3, at over 10 teeth), “presence of gum pockets” (0, none; 1, at up to 3 teeth; 2, at 4 to 10 teeth; 3, at over 10 teeth), “loose teeth” (0, no, never; 1, I had loose teeth in the past; 2, yes, I currently have loose teeth), “tooth extractions because of inflammation and deep gum pockets” (0, no; 1, at up to 3 teeth; 2, at 4 to 10 teeth; 3, at more than 10 teeth), “more dentist visits because of inflammation than because of caries” (0, no; 1, yes), “more tooth/gum problems than other persons of the same age and sex” (0, less than others or comparable to others; 1, more than others; 2, a lot more than others), “inflammation of the gums/bleeding” (0, never; 1, every few years; 2, in many years; 3, (nearly) every year), “magnitude of suffering from dental problems in total during the last 6 months” (0, not at all; 1, a little bit; 2, quite a bit; 3, severe problems), “cold- or heat sensitivity” (0, no, never; 1, yes, in the past; 2, yes, currently) and “use of antibiotics to treat inflammation in the jaw bone” (0, never; 1, once; 2, two to five times; 3, more than five times). Most of the questions were illustrated with pictures to demonstrate the appearance of a radiograph with receding jawbone for example. The questionnaire is available from the authors upon request.

Dentists’ assessment

Patients were asked for the permission to contact their dentists. For all patients who returned a written consent, their dentists were then contacted by mail. They were asked to report whether or not the patient had been diagnosed with PD and to assess the PD status semi-quantitatively with the possible answers “no”, “mild (< 30% bone loss)”, “moderate (30–50% bone loss)” or “severe PD (> 50% bone loss)”. Additionally, the number of teeth was reported. Furthermore, the dentists were asked to send any radiographs not older than 5 years for evaluation, if available.

The obtained radiographs were scored independently by three dentists at the School of Dentistry at the University of Birmingham, UK. The dentists were blinded to the clinical data of the patients. Disagreements were resolved by discussion. The confidence in the diagnosis of PD based on the available radiographs was rated as “certain”, “pretty certain” or “uncertain”.

The PD status reported by the patients’ dentists was defined as the reference standard for PD for all analyses.

Statistical analysis

Correlations between the patient-reported items, the dentists’ assessment and the blinded external assessment of the radiographs were analysed using Spearman’s correlation coefficient. Confirmatory factor analysis was used to test the one-dimensional factor structure of the questionnaire. Items with similar content may result in correlated measurement errors [15] as indicated by large modification indices. Therefore, correlated residuals were assumed in the confirmatory factor model to avoid this method error. The evaluation of the model fit was based on the cut-offs as recommended by Hu and Bentler [16] (root mean square error of approximation (RMSEA) ≤ 0.06, comparative fit index/Tucker-Lewis index (CFI/TLI) ≥ 0.9).

These items were used to calculate a final score for the detection of PD. Since age strongly correlates with the number of teeth and the probability to have PD, we always included age in the score [1].

The diagnostic properties of the score were evaluated by determining the sensitivity, specificity and the area under the receiver operator characteristic curve (AUC). Possible values for the AUC range from 0.5 to 1: 0.5

meaning a random classification of patients as having PD or not and 1 meaning perfect discrimination of the score between the groups. As the PD status was not assessed binary but with several levels of severity, different classifications of patients were performed. This resulted in three binary classifications of PD status: no versus mild/moderate/severe PD, no/mild versus moderate/severe PD and no/mild/moderate versus severe PD. To include all classifications of PD into a single model, an ordinal regression was performed so that it was possible to use the resulting score to assign patients to the most likely level of PD without having to choose which severity of PD should be detected.

Correction for overoptimism

The AUCs resulting from applying the model based on the whole dataset on the same data are likely too optimistic. We corrected for this overoptimism with bootstrap methodology. For 500 bootstrap samples of the size of the original dataset, models for the PD score were estimated. The resulting models were applied to both the original dataset and the respective bootstrap samples. Differences in the resulting AUCs were calculated, resulting in an estimator for the mean overoptimism. This estimator was subtracted from the original AUCs, resulting in bias-corrected AUCs. Additionally, the models based on the dentist's assessment of PD were applied to the subsample of patients with a radiographic assessment of PD, using this as the reference standard.

Results

Study participation and baseline characteristics

A total of 512 patients completed the patient questionnaire and gave permission to contact their dentists. We received 353 data sets with the dentist's assessments of the PD status and 253 data sets with additional radiographs. Radiographs of 4 patients were excluded due to insufficient quality. Figure 1 shows a flowchart of the respective patient numbers. The clinical characteristics at baseline of the different patient groups are shown in Table 1. The subgroups were comparable to the CAPEA cohort except for a slightly higher mean number of teeth in the patients with available radiographs.

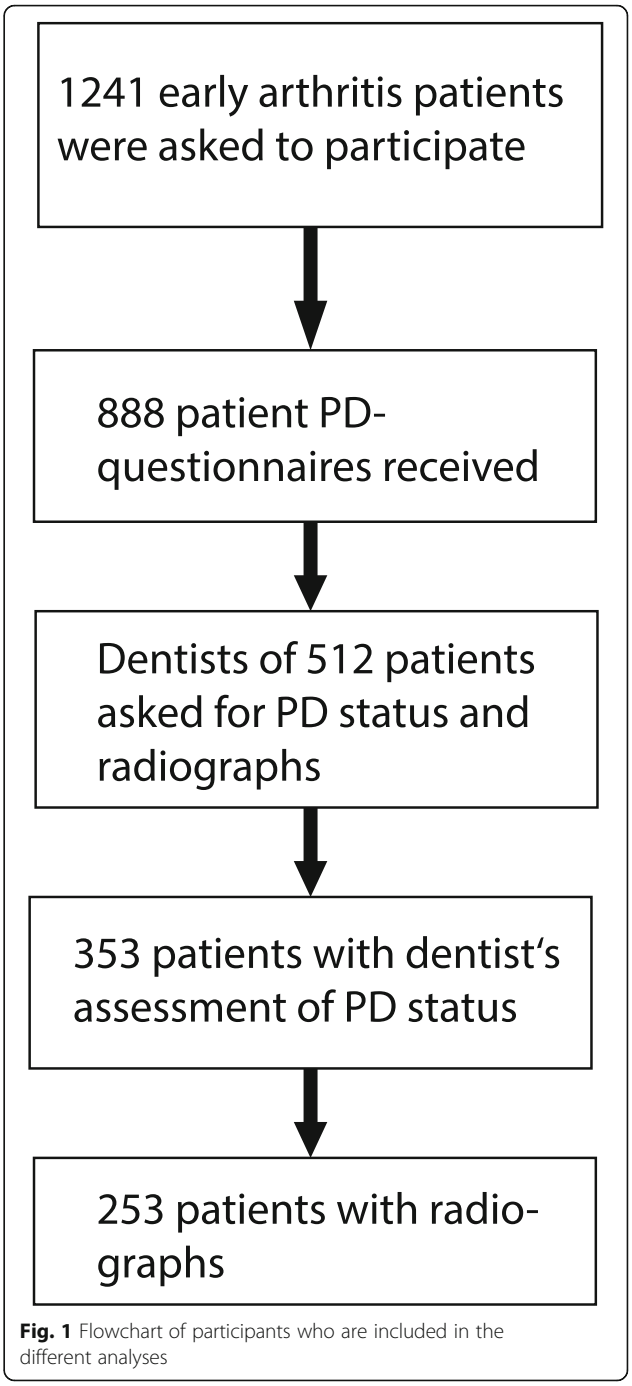

Fig. 1 Flowchart of participants who are included in the different analyses

PD assessments

According to their dentists, 30% of the patients had no, 33% mild, 26% moderate and 11% severe PD. Of the 253 patients with radiographic evaluations, 23% had no, 25% mild, 29% moderate and 23% severe PD. For 41% of the patients, the three independent dentists rated the security of their PD assessment as certain; in 49% of cases, they were moderately certain; and in 11% of cases, they were uncertain, meaning that at least two dentists rated the PD status of the respective patients as uncertain. Certainty was higher for the assessment of no or severe PD than for the assessment of mild or moderate PD.

The correlations between the patient-reported items and the dentists' assessments of PD are shown in Table 2. They were highest for the patient-reported number of teeth, receding jaw bone, receding gums, presence of gum pockets and loose teeth. Those items also correlated highest with the independent assessment of PD via radiographs. The strength of the correlation is only moderate with the highest correlation coefficient of –

Table 1 Baseline characteristics

Variable	All CAPEA patients ($n = 1241$)	PD module patients ($n = 512$)	Patients with dentist's assessment ($n = 353$)	Patients with radiograph ($n = 253$)
Age, years	56.2 (14.3)	56.3 (14)	55.8 (13.3)	55.8 (13.3)
Sex, female	65% (821)	67% (575)	64% (250)	67% (170)
DAS28 ESR	4.7 (1.4)	4.8 (1.4)	4.7 (1.4)	4.7 (1.4)
ESR, mm/h	31.2 (23.4)	31.8 (23.7)	31 (22.9)	30 (22)
CRP, mg/l	18.9 (31.9)	17.8 (28.4)	16.7 (22.3)	15.5 (21.4)
Number of teeth	19.2 (9.6)	19.4 (9.6)	20.8 (8.3)	21.1 (7.7)
SJC28	6 (5.2)	6 (5.2)	5.6 (4.8)	5.4 (4.7)
TJC28	9.7 (6.2)	9.5 (6)	9.2 (5.9)	9.1 (5.8)
RF positive	43% (539)	43% (370)	44% (169)	40% (103)
Anti-CCP positive	39% (493)	38% (331)	40% (157)	36% (93)
Currently smoking	33% (413)	29% (254)	27% (105)	25% (65)

Baseline characteristics of all patients from the early arthritis cohort CAPEA, patients who completed the PD-module, patients with additional dentist's assessment of PD and patients with radiographs

CAPEA Course And Prognosis of Early Arthritis, *PD* periodontitis, *RF* rheumatoid factor, *SJC* swollen joint count, *TJC* tender joint count, *ESR* erythrocyte sedimentation rate, *DAS28* Disease Activity Score including 28 joints, *CRP* C-reactive protein

0.49 between the number of teeth and the dentist's assessment of PD.

Selection of variables for the patient-reported PD score

The factor structure of two models was tested by confirmatory factor analysis (CFA): (a) a one-factor model in which all items were included and (b) a one-factor model in which six items were included (number of teeth, receding jaw bone, receding gums, presence of gum pockets, loose teeth, tooth extractions because of inflammation and deep gum pockets), which correlated among each other in preliminary analyses. The CFA including all questionnaire items did not result in an acceptable model fit (RMSEA = 0.096, CFI = 0.86, TLI = 0.88, WRMR = 0.96). The model that included six selected items did not fit the data well (RMSEA = 0.148, CFI = 0.89, TLI = 0.82, WRMR = 1.05). The modification indices suggested correlated residuals between the items "number of teeth" and "loose teeth" (modification indices = 26.5). The resulting model with correlated residuals yielded an acceptable model fit (RMSEA = 0.06, CFI = 0.94, TLI = 0.90, WRMR = 0.77).

Results from the binary models

Six variables (number of teeth, receding jaw bone, receding gums, presence of gum pockets, loose teeth, tooth

Table 2 Correlations of questionnaire items with PD assessments

Patient questionnaire item	Number of missing values	Spearman's corr. with dentist's assessment	Spearman's corr. with assessment of radiographs
Number of teeth	22	− 0.49	− 0.40
Receding jaw bone	25	0.41	0.43
Receding gums	14	0.37	0.33
Presence of gum pockets	16	0.36	0.31
Loose teeth	9	0.36	0.36
Tooth extractions because of inflammation and deep gum pockets	13	0.27	0.22
More dentist visits because of inflammation than because of caries	12	0.26	0.17
More tooth/gum problems than other persons of the same age and sex	22	0.19	0.10
Inflammation of the gums/bleeding	8	0.12	0.08
Magnitude of suffering from dental problems	6	0.11	0.07
Cold- or heat sensitivity	6	0.09	0.08
Use of antibiotics	6	0.08	0.13

Correlations of questionnaire items with dentists' assessment of PD and with an independent assessment of PD via radiographs. Items in italics were found to be the most suitable to detect PD via factor analysis and are included in the final score

extractions because of inflammation and deep gum pockets) were identified as having a prognostic value for PD. These variables and three additional demographic variables (age, sex and formal education) were used to calculate several binary scores for the assessment of PD. As there are three possible levels of disease severity, several results have to be considered for every possibility to classify patients with the score.

The item which correlated best with the different assessments of PD was the number of the remaining teeth. Therefore, the first proposed possibility to classify patients was to use only age and the self-reported number of the remaining teeth. This resulted in a sensitivity of 86/80/86% (no versus mild, moderate or severe PD/no or mild versus moderate or severe PD/no, mild or moderate versus severe PD), a specificity of 49/64/78% and an AUC of 0.73/0.78/0.86 (Table 3). For all models, the bias-corrected AUCs are only marginally lower. The AUCs of the models based on the dentist's assessment applied to the radiograph scoring data differ most from the original model for the two models in which severe PD is detected (0.66 versus 0.85 and 0.77 versus 0.90).

When using all items from the patient questionnaire that were identified as being useful for the classification of PD, all models improved the diagnostic properties compared to the simple model only using age and the number of teeth. The AUCs of these models range between 0.82 and 0.92 depending on the severity level of PD that shall be detected. The models including sex and formal education of the patients did not show more favourable properties than those only including age as a demographic variable (data not shown). Therefore, sex and formal education were not included in the score.

Results from the ordinal regression model

For the ordinal regression model, there was again a simple version with only the number of teeth and age, and one model including the five additional patient-reported items mentioned above. A likelihood ratio test showed that the model with the additional items is better than the simple version.

The following were the results for the score:

PD score = 2.8 + 0.033 × age + 0.37 × gum pockets + 0.30 × receding gums + 0.45 × loose teeth + 0.84 × receding jaw bone – 0.40 × tooth extractions – 0.12 × number of teeth.

The cut-offs were 1.83 for mild PD, 3.91 for moderate PD and 6.26 for severe PD. For example, a patient with an age of 40 years, no reported tooth or gum problems and all 28 teeth would have a score of 2.8 + 1.32–3.36 = 0.76 and would be classified as having no PD.

The following were the results for the simple version of the score:

PD score (simple version) = 2.5 + 0.036 × age – 0.11 × number of teeth. The corresponding cut-off values were 1.16 for mild PD, 2.88 for moderate PD and 4.91 for severe PD.

Table 4 shows the classification of the patients by the score compared to the reference standard. Patients with severe PD are only detected in less than 30% of the cases and most often classified as "moderate" (Table 5).

The longer version of the score had considerably more specificity for the detection of PD than the short version (57% versus 40%). It also had a higher sensitivity for detecting moderate or severe PD.

Discussion

A patient-reported questionnaire to detect PD in patients with RA was developed. Six patient-reported items were selected to build the age-adjusted score. The score had a fair sensitivity to detect mild, moderate or severe versus no PD and was very specific at excluding severe PD. Additionally, a simple score including only age and the number of teeth was evaluated. This score might be

Table 3 Diagnostic properties of logistic regression models

Model	Severity of detected PD	Reference standard: dentist's assessment			Bias-corrected AUC	AUC of the original model applied on radiograph scoring data
		Sensitivity (%)	Specificity (%)	AUC		
Age + number of teeth	Mild, moderate or severe versus no	86.0	48.6	0.73	0.73	0.82
	Moderate or severe versus no or mild	80.3	64.1	0.78	0.77	0.72
	Severe versus no, mild or moderate	86.1	78.1	0.86	0.85	0.66
Age + 6 patient-reported items	Mild, moderate or severe versus no	64.2	88.5	0.82	0.81	0.88
	Moderate or severe versus no or mild	72.8	80.7	0.85	0.83	0.83
	Severe versus no, mild or moderate	96.6	81.5	0.92	0.90	0.77

Sensitivities, specificities and AUCs to detect different levels of severity of PD in the simple model and in the model including six questionnaire items. The table also shows the AUCs of these models after correction for overoptimism with bootstrap methods and the AUCs of the models if the independent assessment of PD with radiographs is used as a reference standard

Table 4 Concordance of score and dentist's assessment

Classification of PD by score (age + 6 patient-reported items)	Dentist's assessment of PD				
	No	Mild	Moderate	Severe	Total
No	55	29	2	0	86
Mild	32	51	34	2	119
Moderate	9	21	37	19	86
Severe	0	0	1	8	9
Total	96	101	74	29	300

Comparison of classification of PD with the help of the PD score and the reference standard

useful if PD shall be studied in a setting where it is only feasible to ask one additional question considering PD. The simple version also had a high sensitivity for detecting at least mild PD and a very good specificity to exclude severe PD. The overall properties of the score with six patient-reported items were more favourable than those of the simple score. The AUCs of 0.81, 0.83 and 0.90 respectively for the detection of at least mild, at least moderate or severe PD were comparable to those found by Dietrich et al. [11], Gilbert and Litaker [10] and Taylor and Borgnakke [17] and a little bit higher than those found by Genco et al. [9] (AUC of 0.76 for the detection of severe PD in the myocardial infection periodontitis study). In contrast to these questionnaires for self-reported PD, our score does not include sex or formal education. This might be due to the different study collectives with this study only including RA patients and the other studies including patients from the general population those who had a myocardial infarction.

Compared to the questionnaire used by Coburn et al. [13] that was also evaluated on RA patients, our questionnaire had a better AUC for the detection of severe PD (0.79 versus 0.90). For the detection of mild or moderate PD, the AUCs were comparable. In the investigation by Coburn et al., patients received a full-mouth periodontal examination to determine their PD status, while in the CAPEA periodontitis project, the patients' dentists were asked to grade the severity of their patient's PD semiquantitatively. This shows that in a setting where the diagnosis for PD was more standardised and clinically evaluated, the resulting PD score still does not have more favourable properties.

The items included in this score had some overlap with those identified by Dietrich et al. [11] (loosening of teeth, dentist told patient had lost bone around his or her teeth) but also included the presence of gum pockets and bleeding gums which are not represented in the final models of Dietrich et al., Taylor and Borgnakke [17] and Gilbert and Litaker [10] (in Gilbert's score, a more general rating of "gum health" is included, though). There was also an overlap with the items used by Coburn et al. [13]. Items concerning bleeding gums, bone loss, deep pockets, loose teeth and oral surgery were also included in our questionnaire in a similar way. While "bleeding gums" was not included in the final PD score in our analysis; the parameter correlating best with PD in our analysis (number of teeth) was not included in Coburn et al.'s questionnaire.

One limitation of this study is that our reference standard to determine a patient's PD status is the report of the patient's individual dentist and was not evaluated by a study dentist. To validate the diagnosis, the radiographs were assessed externally by three independent dentists. If the PD score we developed is applied to these data, the AUCs are in the range of 0.77 to 0.88 which means that if an objective blinded assessment of PD is used as a reference standard, the questionnaire also performs reasonably well. While there were more male than female patients participating in the Coburn study, CAPEA patients form a representative sample of early arthritis patients in Germany with more female patients.

The sensitivity and specificity of the CAPEA PD questionnaire are reasonably good. In order to conduct large epidemiologic trials that further investigate the relationship between RA and PD, instruments with a high accuracy would be needed. The misclassification rate might be too high to assess the relationship between clinical features of RA and periodontal status, if the periodontal status is determined through a patient-reported questionnaire alone. This problem could partly

Table 5 Diagnostic properties for ordinal regression model

Model	Severity of detected PD	Sensitivity (%)	Specificity (%)
Age + number of teeth	Mild, moderate or severe versus no	91.7	39.6
	Moderate or severe versus no or mild	49.5	85.8
	Severe versus no, mild or moderate	20.7	100
Age + 6 patient-reported items	Mild, moderate or severe versus no	84.8	57.3
	Moderate or severe versus no or mild	63.1	84.8
	Severe versus no, mild or moderate	27.6	99.6

Sensitivities and specificities for the detection of different levels of PD with the score derived from the ordinal regression model

be solved by using a continuous measure of PD instead of categorising patients to "no", "mild", "moderate" or "severe" PD. Using the PD score as a continuous measure would still allow investigating the correlation between the severity of clinical measures of RA and PD with less misclassification errors than when using the categorisation.

Conclusions

The CAPEA PD score can be used as a measure of PD in epidemiological settings. In a categorical analysis using cut-off values, researchers should keep in mind, however, that this score does show only moderate diagnostic properties. If high accuracy is not essential, the number of teeth and age alone can also be used as a simple measure for the detection of the frequency of PD in patients with RA.

Abbreviations

Anti-CCP: Anti-citrullinated protein; AUC: Area under the receiver operator characteristic curve; CAPEA: Course And Prognosis of Early Arthritis; PD: Periodontitis; CFA: Confirmatory factor analysis; CFI/TLI: Comparative fit index/Tucker-Lewis index; CRP: C-reactive protein; DAS28: Disease Activity Score including 28 joints; ESR: Erythrocyte sedimentation rate; RF: Rheumatoid factor; RMSEA: Root mean square error of approximation; SJC: Swollen joint count; TJC: Tender joint count; WRMR: Weighted root mean square residual

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Authors' contributions

All authors drafted the article, revised it critically for important intellectual content and approved the final version to be published. JC had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. AZ and TD were involved in the study conception and design. MC and JC were responsible for the acquisition of the data. JC, TD, MC, JK and AZ were involved in the analysis and interpretation of the data.

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Availability of data and materials

The datasets analysed during the current study are not publicly available, because we respect our patient's right to privacy. Consent for publication of the dataset has not been asked at the point of recruitment to the trial.

Ethics approval and consent to participate

Ethical approval was obtained from the Ethics Committee of the Charité University Medicine, Berlin.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

2.4. Komorbiditäten bei systemischem Lupus erythematodes

Auch beim systemischen Lupus erythematodes spielen Komorbiditäten eine wichtige Rolle. Häufige Komorbiditäten sind renale und kardiovaskuläre Erkrankungen. Insbesondere kardiovaskuläre Erkrankungen wie z.B. Bluthochdruck und koronare Herzkrankheit sind in der Normalbevölkerung auch weit verbreitet. In der folgenden Arbeit wurde anhand von Abrechnungsdaten der Barmer Krankenkasse untersucht, von welchen Komorbiditäten Personen mit inzidenter Diagnose eines systemischen Lupus betroffen sind.

Der nachfolgende Text entspricht dem Abstrakt der Arbeit:

> Albrecht K, Redeker I, Aringer M, Marschall U, Strangfeld A, Callhoff J. Comorbidity and healthcare utilisation in persons with incident systemic lupus erythematosus followed for 3 years after diagnosis: analysis of a claims data cohort. Lupus Sci Med. 2021;8(1) https://doi.org/10.1136/lupus-2021-000526

Abstract

Objective To analyse comorbidity and healthcare utilisation in individuals with SLE.

Methods A cohort of individuals with incident SLE diagnosis in 2016 were investigated using claims data from a German statutory health insurance fund. Concomitant diagnoses, medical prescriptions, hospitalisation and sick leave were analysed in the year prior to diagnosis and during a 3-year follow-up in comparison with age-matched and sex-matched controls (1) without autoimmune diseases and (2) with incident diabetes mellitus. Sensitivity analyses were performed excluding cases with additional autoimmune diagnoses and without prescription of antimalarials.

Results Among 571 individuals with SLE, hypertension (48%), depression (30%), hyperlipidaemia (25%), osteoarthritis (25%) and osteoporosis (20%) were the most frequent comorbidities in 2016. Cerebrovascular disease was documented in 9.6%. The number of drugs (mean 9.6, Δ+6.2), hospitalisation (40%, Δ+27%) and days on sick leave (median 46 days, Δ+27 days) increased significantly in the first year with SLE diagnosis. Individuals with SLE were more frequently hospitalised and had more medications compared with both control groups (all $p<0.001$). The increase in comorbidity diagnoses was low in controls without autoimmune diseases, while controls with diabetes showed a more pronounced increase in cardiovascular risk factors, but less in osteoporosis and cerebrovascular disease. Sensitivity analyses showed comparable results.

Conclusion Comorbidities are frequently detected at the time of diagnosis of SLE. High numbers of drug prescriptions and hospitalisation following SLE diagnosis reflect the comprehensive disease burden. The comparison with incident diabetes shows that differences with controls without autoimmune disease are overestimated by detection bias.

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Comorbidity and healthcare utilisation in persons with incident systemic lupus erythematosus followed for 3 years after diagnosis: analysis of a claims data cohort

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ABSTRACT

Objective To analyse comorbidity and healthcare utilisation in individuals with SLE.

Methods A cohort of individuals with incident SLE diagnosis in 2016 were investigated using claims data from a German statutory health insurance fund. Concomitant diagnoses, medical prescriptions, hospitalisation and sick leave were analysed in the year prior to diagnosis and during a 3-year follow-up in comparison with age-matched and sex-matched controls (1) without autoimmune diseases and (2) with incident diabetes mellitus. Sensitivity analyses were performed excluding cases with additional autoimmune diagnoses and without prescription of antimalarials.

Results Among 571 individuals with SLE, hypertension (48%), depression (30%), hyperlipidaemia (25%), osteoarthritis (25%) and osteoporosis (20%) were the most frequent comorbidities in 2016. Cerebrovascular disease was documented in 9.6%. The number of drugs (mean 9.6, Δ+6.2), hospitalisation (40%, Δ+27%) and days on sick leave (median 46 days, Δ+27 days) increased significantly in the first year with SLE diagnosis. Individuals with SLE were more frequently hospitalised and had more medications compared with both control groups (all $p<0.001$). The increase in comorbidity diagnoses was low in controls without autoimmune diseases, while controls with diabetes showed a more pronounced increase in cardiovascular risk factors, but less in osteoporosis and cerebrovascular disease. Sensitivity analyses showed comparable results.

Conclusion Comorbidities are frequently detected at the time of diagnosis of SLE. High numbers of drug prescriptions and hospitalisation following SLE diagnosis reflect the comprehensive disease burden. The comparison with incident diabetes shows that differences with controls without autoimmune disease are overestimated by detection bias.

Key messages

What is already known about this subject?

- Patients with SLE have a high burden of comorbidity.

What does this study add?

- Numerous comorbidities are frequently detected at the time of SLE diagnosis.
- Increasing rates of medical prescriptions, hospitalisation and sick leave demonstrate comprehensive disease burden in the first 2 years after SLE onset.
- Cerebrovascular disease was diagnosed in every tenth individual at the time of lupus diagnosis.

How might this impact on clinical practice or future developments?

- Comorbidity assessment is essential already at the onset of SLE.
- Detection bias needs to be considered when comparing data of persons with chronic diseases with controls using claims data.

INTRODUCTION

SLE is a systemic autoimmune disease which by nature is prone to lead to manifold organ involvement. Comorbidity in SLE is common, occurring as a consequence of chronic inflammation, organ damage, anti-inflammatory therapy and psychosocial effects. Data from the UK indicate a great burden of comorbidity in people with SLE compared with population controls.[1] An increased risk of numerous comorbidities is already present prior to diagnosis but also remains in the further course of the disease.[2] The European League Against Rheumatism (EULAR) recommendations for the management of SLE address the importance of assessing cardiovascular and infectious risk factors in SLE.[3] In addition, bone health is considered a major comorbidity target.[4 5] So far, there have been only limited data on comorbidities in people with SLE in Germany. Patients with SLE who are treated in specialised arthritis centres are documented in the German

National Database[6]; however, majority of patients have long-standing disease and numbers on incident SLE cases are small.[7 8] The German LuLa study, the second relevant cohort in Germany, focuses on self-reported outcomes instead.[9] A recent claims data analysis from a German health insurance fund database has identified a rising incidence of SLE diagnoses accompanied by an increase in healthcare resource utilisation and costs.[10] The approach for this study was to use health insurance data to approximate the frequencies of comorbidity diagnoses in SLE in comparison with population-related controls.[11] SLE and comorbidity-related drug prescriptions, sick leave and hospitalisation were examined in individuals with incident SLE diagnosis in the year prior to diagnosis and during a 3-year follow-up in comparison with age-matched and sex-matched controls.

PATIENTS AND METHODS

Definition of SLE diagnosis in claims data

A cohort of persons with incident SLE diagnosis was created using data from a large nationwide statutory health insurance fund (BARMER). In Germany, around 90% of the population are insured in one of the statutory health insurance companies. The other 10% are insured in private health insurance companies. The BARMER data cover around 11% of the German population from all areas of Germany and are representative of the German population in terms of socioeconomic status. There are more women older than 50 than in the general population and less men younger than 50. Insurance fees between the different German statutory health insurances differ only marginally.

Individuals aged ≥18 years were identified based on SLE diagnosis (M32.1: SLE with organ or systemic involvement; M32.8: other forms of SLE; M32.9: SLE, unspecified),[12] according to the German modification of the International Statistical Classification of Diseases (ICD-10). To identify incident cases, two outpatient or one inpatient diagnosis was required to be present in 2016, 2017 and 2018 but not in the 2 previous years (2014 and 2015). This cohort was analysed in the year prior to diagnosis (2015), the index year (2016) and for 2 consecutive years (2017 and 2018). Persons with SLE diagnoses recorded in 2014 and 2015 and persons who were not continuously insured from 2014 to 2018 or did not have an SLE diagnosis in at least two quarters in 2017 and/or 2018 were excluded (see flow chart in figure 1). Persons with drug-induced SLE (M32.0; n=83 in 2016) were also excluded from the analysis. To reduce misclassification related to sporadic diagnoses, we selected a stricter requirement of at least two ICD-10 diagnoses in each of the years from 2016 until 2018 than usually performed.[10–12]

We performed a sensitivity analysis of the diagnosis validation. We further analysed the accuracy of identifying patients with SLE in the claims database following the validation algorithm of Schwarting *et al*,[10] which includes primary diagnosis in hospital, outpatient diagnosis by a specialised physician, performance of laboratory ANA tests, antimalarial or immunosuppressive medication, or organ involvement in any of the years 2016, 2017 or 2018.

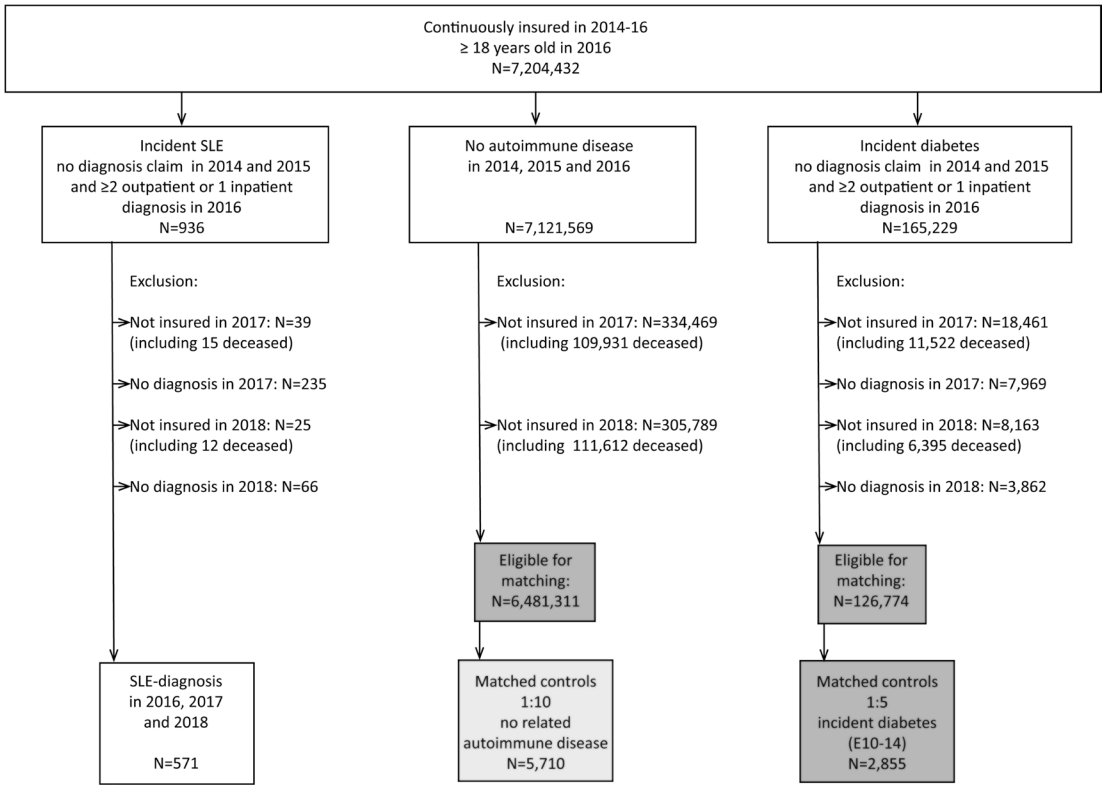

Figure 1 Flow chart.

Characterisation of the SLE cohort

The mean age and proportion of women were calculated in the index year. Rheumatology care was identified by the medical specialist number and by identifying those physicians who used claims codes exclusive to rheumatologists. All patients who visited a rheumatologist at least once in the corresponding year were considered to be rheumatologically treated. Diagnostic ANA testing was analysed using the claims codes from the German evidence-based medicine catalogue. Organ manifestations that are specifically assigned or related to SLE were identified by ICD-10 codes. The codes can be referenced in online supplemental table 1: glomerulonephritis, pericarditis, endocarditis, cerebral arteritis, dementia, encephalitis, polyneuropathy, myopathy, lung involvement, Raynaud's syndrome and antiphospholipid syndrome. Anti-inflammatory therapies were identified via the Anatomical Therapeutic Chemical Classification (ATC). ATC codes are shown in online supplemental table 1: glucocorticoids, (hydroxy)chloroquine, azathioprine, methotrexate, mycophenolate mofetil, ciclosporin, leflunomide, belimumab, rituximab and abatacept. For biologics and cyclophosphamide, procedure codes for administration in hospital were also considered.

Comparison of outcomes derived from claims data

Comorbidity diagnoses were identified by ICD-10 codes. The codes are shown in online supplemental table 1: hypertension, hyperlipidaemia, obesity, cerebrovascular diseases, thrombosis, renal disease, chronic obstructive pulmonary disease, hypothyroidism, osteoarthritis, osteoporosis (total, with and without pathological fracture), fibromyalgia, depression, polyneuropathy, solid tumour and metastatic cancer. Where applicable, definitions from the Elixhauser comorbidity score were used, and the Elixhauser score was calculated.[12] Specialist care on comorbidities was identified by medical specialist numbers. Lipid profile testing was used to detect differences in the frequency of comorbidity screening and was identified from the German evidence-based medicine catalogue.

Using inpatient data from the hospital claims data, persons were counted as being hospitalised in the corresponding year if they had at least one inpatient admission. Sick leave and days of sick leave were assessed for each corresponding year. For sick leave, only persons <65 years (corresponding to the German retirement age applicable for the years analysed) were included. Since the occupational status was not available, the average duration was calculated and reported in median days instead of the proportion of persons with sick leave. To count the days on sick leave for the corresponding year, sick leave periods starting before 1 January or ending after 31 December were cropped so that the maximal possible number of days on sick leave was 365 days.

The mean number of prescribed medications including SLE anti-inflammatory therapy was calculated. Medical prescriptions related to comorbidity were identified by ATC codes (the codes are listed in online supplemental table 1: cardiovascular therapy (antihypertensives, beta-blockers, diuretics), lipid-lowering therapies, osteoporosis therapies, antidepressants, non-steroidal antirheumatic drugs (NSAIDs), other analgesics and opioids. As prescriptions are not assigned to a specific diagnosis, symptomatic pain medications including NSAIDs were listed here and not as lupus-specific therapy.

The data cover all medications for which costs are payed by the health insurance. This generally includes all medications we analysed in this manuscript, and also those that could be bought over the counter (such as ibuprofen), but were prescribed by a physician. Copayments are generally small, and for people with a chronic illness such as SLE there is a limit of 1% of the patient's gross income per year. After a person has reached this limit, there are no copayments anymore.

Statistical analysis

Control groups

To compare the frequency of comorbidity claims, drug prescriptions, sick leaves and hospitalisations, a control group was randomly selected and matched 10:1 for age and sex from the insurance population without SLE and without any of the following rheumatic diseases: rheumatoid arthritis (M05, M06), myositis (M33), systemic sclerosis (M34), Sjögren's syndrome (M35.0) and mixed connective tissue disease (M35.1). To account for a possible detection bias in persons with incident diagnoses compared with controls without, a second control group with an incident diagnosis of diabetes (ICD-10: E10–E14) was randomly selected and matched 5:1 for age and sex to the SLE cohort. Diabetes was selected for comparison in the expectation that comparable comorbidity screening is performed at the time of diagnosis, and with regard to cardiovascular risk factors in particular. Persons in the control groups also had to be continuously insured between 2014 and 2018 (figure 1). In the diabetes control group, diagnostic codes of diabetes had to be documented in at least two quarters of each year (2016, 2017 and 2018), but no codes were allowed to be present in 2014 and 2015, analogue to the SLE cohort.

The frequencies of comorbidities in 2016 were compared with χ^2 test or Fisher's exact test, as appropriate. Elixhauser scores and the number of prescribed medications were compared with Wilcoxon-Mann-Whitney-tests.

To exclude cases with uncertainty in SLE diagnosis, two sensitivity analyses were performed excluding (1) cases with additional diagnosis of Sjögren's syndrome, systemic sclerosis, mixed connective tissue disease or tubulointerstitial kidney disease and (2) without prescription of hydroxychloroquine (HCQ), considering that HCQ is recommended as standard therapy for SLE.

Patient and public involvement

Within the framework of the Targeted Risk Management in Muskuloskeletal Diseases (TARISMA) research project, patient partners were involved in the reporting of our research.

RESULTS

Characteristics of individuals with incident SLE

Out of 7 204 432 persons ≥18 years who had been continuously insured from 2014 to 2016, a total of 571 persons had incident SLE diagnosis in 2016 and a prevalent SLE diagnosis in 2017 and 2018 (figure 1). A total of 159 persons had an inpatient discharge diagnosis. Outpatient SLE diagnosis was documented by a specialised physician in 325 persons. Between 2015 and 2018, ANA tests were coded in 360, 457 received antimalarial or immunosuppressive medication, 86 had ICD diagnosis of organ involvement, and 320 (56 %) were seen by a rheumatologist. Altogether, 519 of the 571 incident SLE cases in this analysis (90.9%) fulfilled at least one Schwarting validity criterion.

The mean age in the year of SLE diagnosis was 55.1 years (6% 18–30 years, 32% 31–50 years, 46% 51–70 years, 16% >70 years) and 87% were female. SLE-associated organ involvement was rarely documented, with the most frequent ICDs being antiphospholipid syndrome (7%) and kidney involvement (6%).

Drug prescriptions related to SLE diagnosis

Glucocorticoids were prescribed to 55% of all individuals with SLE in the first year after diagnosis (figure 2). Three in four persons (75%) of the incident SLE cohort did not have any prescription of glucocorticoids between 2005 and 2015. Antimalarials (49%), azathioprine (13%), methotrexate (11%) and mycophenolate (8%) were started in the index year or year 1, while rituximab (1.4%) was mainly introduced in year 1, and belimumab (3.5%) in year 1 and year 2 after diagnosis (figure 2). Seven persons (1.2%) received cyclophosphamide in the index year.

Comorbidity diagnoses

Among individuals with SLE, the mean Elixhauser comorbidity score increased from 1.1 in 2015 to 4.5 in the year of diagnosis. Hypertension (48%), depression (30%), hyperlipidaemia (25%), osteoarthritis (25%) and osteoporosis (20%) were the most frequent comorbidity diagnoses in 2016. Most of the osteoporosis diagnoses were documented as osteoporosis without pathogenic fracture. The proportion of SLE cases with osteoporotic fracture was much higher than in the controls (4.7% in 2016 in SLE vs 1.0%/1.1% in controls). Cerebrovascular disease was documented in 9.6% of individuals in the year of the first SLE diagnosis. A relevant increase of comorbidity diagnoses in the index year was present particularly in cardiovascular risk factors, cerebrovascular disease, kidney disease, musculoskeletal disorders, depression, hypothyroidism and solid tumours (table 1). After that, the number of comorbidity diagnoses increased only slightly in year 1 and year 2 after SLE diagnosis.

1. In controls without related autoimmune diseases (n=5710), the number of comorbidity diagnoses only slightly increased in the index year (Elixhauser Δ+0.3). All comorbidity diagnoses except metastatic cancer were significantly more frequent in cases with SLE in the index year compared with the controls (p values are reported in table 1).
2. In controls with incident diabetes, cardiovascular risk factors increased to a higher extent and osteoarthritis, osteoporosis, cerebrovascular disease and depression to a lower extent compared with cases with SLE (figure 3). Cerebrovascular disease, thrombosis and kidney disease were significantly more frequent in individuals with SLE compared with controls with diabetes in the index year (all <0.001; table 1).

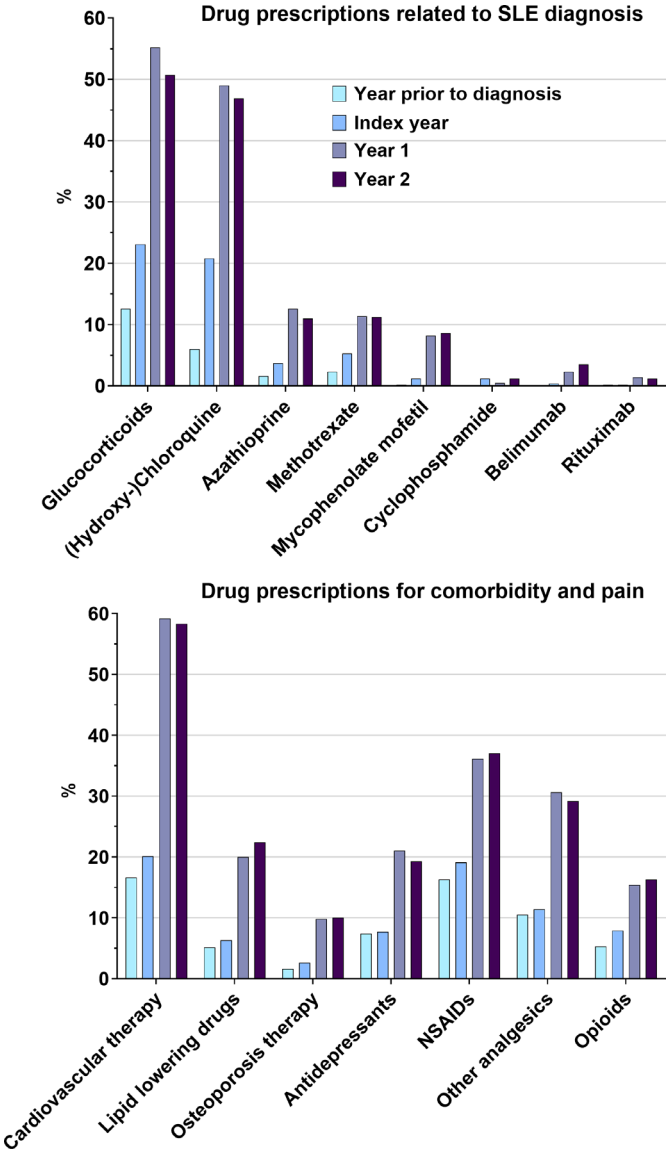

Figure 2 Drug prescriptions in persons with incident SLE in 2016. NSAIDs non-steroidal antirheumatic drugs.

Healthcare utilisation

Diagnostics and specialist care regarding comorbid conditions were significantly more frequent in cases with SLE or diabetes compared with controls without autoimmune disease. In the index year, the lipid profile was tested in 43% (controls), 60% (SLE) and 80% (diabetes). In the study period, nephrology care was visited by 17% (SLE)

Table 1 Comparison of SLE cohort and age-matched and sex-matched control groups

	Cohort incident SLE in 2016 (n=571)				Control 1: no autoimmune disease (n=5710)				Control 2: incident diabetes (n=2855)				P value SLE vs controls in 2016	
	2015	2016	2017	2018	2015	2016	2017	2018	2015	2016	2017	2018	1	2
Comorbidity diagnoses														
Elixhauser score, mean	1.1	4.2	4.4	4.5	1.6	1.9	2.0	2.1	0.9	4.1	4.1	4.2	<0.001	0.12
Hypertension	16.1	47.6	50.6	51.8	29.8	34.9	35.9	37.4	15.6	64.1	65.3	66.6	<0.001	<0.001
Hyperlipidaemia	7.2	25.0	26.1	26.4	17.9	21.0	22.0	22.7	7.8	40.1	41.7	41.4	0.03	<0.001
Cerebrovascular disease	2.3	9.6	10.7	11.9	3.5	4.4	5.1	5.3	0.9	6.6	7.4	8.0	<0.001	0.01
Thrombosis	0.7	4.0	4.7	5.1	0.8	1.0	1.1	1.2	0.4	1.6	1.7	1.6	<0.001	<0.001
Kidney disease	2.5	15.2	17.7	17.7	2.4	3.3	3.8	4.5	0.8	7.9	9.2	11.0	<0.001	<0.001
COPD	6.5	24.2	24.5	24.3	9.7	11.1	11.1	11.6	5.4	19.2	19.4	20.2	<0.001	0.006
Hypothyroidism	6.1	18.9	19.1	20.5	10.1	11.2	11.9	12.5	4.4	18.0	19.1	19.5	<0.001	0.59
Osteoarthritis	7.2	25.4	25.4	26.6	11.0	12.9	14.2	14.8	4.0	17.8	19.4	20.2	<0.001	<0.001
Osteoporosis (total)	4.4	20.3	20.8	22.6	4.7	5.4	5.6	5.8	1.5	5.6	6.1	6.2	<0.001	<0.001
Osteoporosis with pathological fracture	0.9	4.7	4.6	5.1	0.8	1.0	1.1	1.1	0.3	1.1	1.3	1.2	<0.001	<0.001
Osteoporosis without pathological fracture	4.2	19.8	20.1	21.5	4.0	4.9	5.2	5.3	1.5	4.9	5.4	5.5	<0.001	<0.001
Fibromyalgia	2.1	6.0	6.3	6.0	0.6	0.8	0.9	1.0	0.5	1.6	1.9	1.9	<0.001	<0.001
Depression	11.9	29.9	31.9	32.6	14.9	17.8	18.7	19.0	7.8	26.2	27.4	28.5	<0.001	0.06
Polyneuropathy	1.8	7.4	9.6	10.2	2.6	3.4	3.7	4.1	0.6	10.8	13.2	14.7	<0.001	0.01
Solid tumour	1.8	7.2	7.7	8.2	4.1	5.1	5.2	5.9	1.3	5.4	6.0	7.1	0.01	0.10
Metastatic cancer	0.4	0.5	1.1	1.1	0.4	0.5	0.5	0.6	0.0	0.7	0.8	1.0	0.91	0.70

Numbers are percentages if not otherwise stated.
COPD, chronic obstructive pulmonary disease.

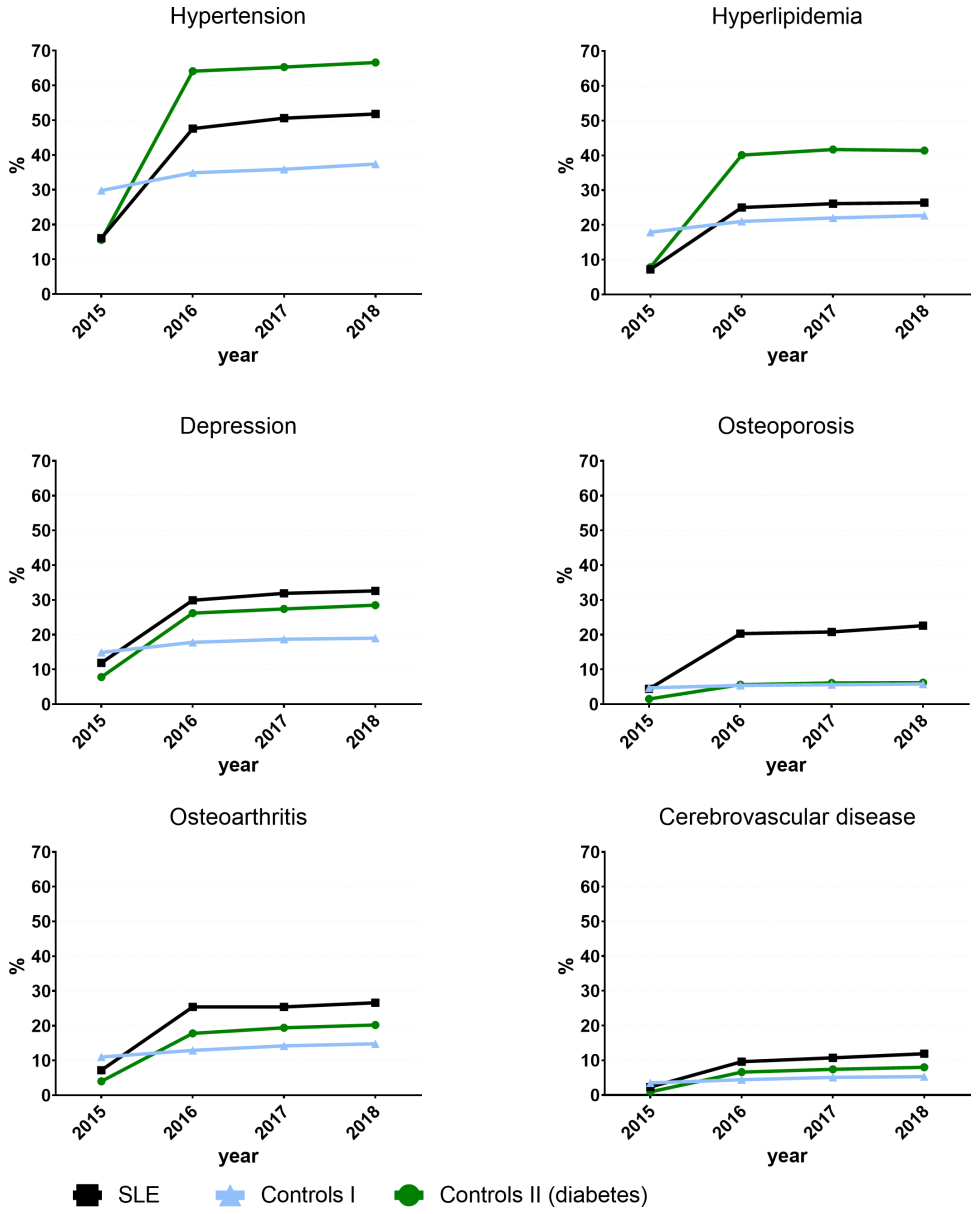

Figure 3 Comorbidity recorded in persons with incident SLE in 2016 (n=571, M32.1, M32.8, M32.9) and age-matched and sex-matched controls (n=5710 without related autoimmune disease, n=2855 with incident diabetes, E10–14).

vs 3% (controls) vs 6% (diabetes), neurology care by 10% (SLE) vs 10% (controls) vs 13% (diabetes), and a psychiatrist by 1%–7% (all groups).

Hospitalisation increased from 13% in the year prior to SLE diagnosis to 40% in the first year after diagnosis. Patients with SLE were significantly more frequently hospitalised compared with both control groups (both p<0.001). There was no relevant increase in controls without autoimmune disease (from 14% to 18%), while hospitalisation also increased from 7% to 25% in patients with diabetes (table 2).

Sick leave

A total of 430 persons with SLE, 4300 controls without related autoimmune disease and 2150 controls with diabetes were <65 years of age. For those who were on sick leave, in the index year the median number of days on sick leave increased compared with the year before diagnosis in cases with SLE (year before diagnosis: 19 days; index year: 46 days) and in controls with diabetes (21 days and 27 days), but not in controls without autoimmune disease (20 days and 14 days).

Drug prescriptions related to comorbidity and pain

In SLE, the mean number of drug prescriptions increased from 3.4 in 2015 to 9.5 in 2018, exceeding the increase in controls (mean from 3.9 to 5.2) and controls with diabetes (from 2.7 to 7.5) (p<0.001). Cardiovascular therapies were prescribed to 58% of persons with SLE, 40% (controls) and 68% (diabetes) in the second year after diagnosis. Prescriptions of NSAIDs and opioids roughly doubled after SLE diagnosis, and prescriptions of other analgesics and antidepressants nearly tripled after SLE diagnosis (figure 2). NSAIDs and opioids were prescribed

Table 2 Comparison of SLE cohort and age-matched and sex-matched control groups

	Cohort incident SLE in 2016 (n=571)				Control 1: no autoimmune disease (n=5710)				Control 2: incident diabetes (n=2855)				P value SLE vs controls in 2016	
	2015	2016	2017	2018	2015	2016	2017	2018	2015	2016	2017	2018	1	2
Specialist care														
Nephrologist	1	14	14	17	1	1	2	3	1	4	4	6	<0.001	<0.001
Neurologist	3	10	8	10	6	6	6	10	3	10	10	13	<0.001	0.98
Psychiatrist	1	4	4	4	2	3	3	6	2	5	5	7	0.09	0.21
Diagnostics														
Lipid profile	20	60	59	58	37	42	42	42	16	80	75	73	<0.001	<0.001
Hospitalisation	13	21	40	36	14	15	18	17	7	10	25	25	<0.001	<0.001
Drug prescriptions														
Mean number of drugs	3.4	4.5	9.6	9.5	3.9	4.0	4.5	6.0	2.7	3.3	7.0	7.5	<0.001	<0.001
Cardiovascular therapy*	16.6	20.1	59.2	58.3	31.7	33.3	38.1	40.2	17.9	20.0	67.0	68.2	<0.001	0.89
Lipid-lowering drugs	5.1	6.3	20.0	22.4	9.9	10.6	12.4	13.4	4.4	7.2	29.7	32.9	<0.001	0.80
Osteoporosis therapy	1.6	2.6	9.8	10.0	1.3	1.4	1.9	2.0	0.3	0.6	1.2	1.2	0.10	<0.001
Antidepressants	7.4	7.7	21.0	19.3	10.8	11.3	12.7	12.5	6.7	6.3	18.8	18.8	0.02	0.22
NSAID	16.3	19.1	36.1	37.0	25.1	25.0	27.0	26.4	12.0	11.8	34.2	34.2	0.002	<0.001
Other analgesics	10.5	11.4	30.6	29.2	12.5	13.0	15.0	15.6	6.0	6.4	22.1	23.5	0.64	<0.001
Opioids	5.3	7.9	15.4	16.3	5.1	5.4	6.0	6.8	2.3	3.2	10.5	11.4	0.004	<0.001

Numbers are percentages if not otherwise stated.
*Antihypertensives, beta-blockers and/or diuretics.
NSAID, non-steroidal antirheumatic drug.

Table 3 Sensitivity analyses of persons without further autoimmune disease and with antimalarial therapy required

	Persons with incident SLE in 2016 and without further autoimmune disease (n=453)				Persons with incident SLE in 2016 and with antimalarial therapy (n=307)			
	2015	2016	2017	2018	2015	2016	2017	2018
Comorbidity diagnoses								
Elixhauser score, mean	1.0	4.1	4.3	4.4	1.2	4.0	4.0	4.2
Hypertension	14.8	46.8	49.2	50.6	16.9	41.0	44.3	45.3
Hyperlipidaemia	7.3	25.8	26.5	26.7	6.8	20.2	20.2	20.2
Cerebrovascular disease	2.2	8.8	9.7	10.6	1.6	7.2	9.4	11.1
Thrombosis	0.7	3.3	3.1	4.0	0.7	4.6	5.2	4.9
Kidney disease	2.4	16.3	18.1	18.3	2.0	12.1	14.3	15.6
COPD	0.7	2.4	3.3	3.1	1.0	3.6	3.9	2.6
Hypothyroidism	6.0	17.0	17.0	18.3	5.5	14.0	15.0	15.6
Osteoarthritis	6.2	23.8	24.1	25.2	7.5	22.5	22.8	23.5
Osteoporosis	3.3	19.0	19.2	20.8	3.6	16.9	17.6	18.9
Fibromyalgia	1.5	6.0	6.0	5.7	2.3	6.2	6.5	5.9
Depression	12.4	30.2	31.8	32.5	13.4	30.9	31.3	32.9
Polyneuropathy	1.8	6.6	8.2	9.1	0.0	0.7	1.0	1.0
Solid tumour	1.8	6.8	7.3	7.9	2.3	6.8	6.8	7.2
Metastatic cancer	0.4	0.7	1.3	1.3	0.3	0.3	0.7	0.0
Specialist care								
Nephrologist	1	12	13	14	2	12	12	13
Neurologist	3	10	8	8	4	9	8	9
Psychiatrist	1	4	4	4	3	4	4	4
Diagnostics								
Lipid profile	19	60	57	57	21	57	56	56
Hospitalisation	13	21	39	34	14	27	40	36
Drug prescriptions								
Mean number of drugs	3.3	4.4	9.4	9.4	3.6	5.0	9.4	9.3
Cardiovascular therapy*	15.5	19.2	57.8	58.1	16.6	21.5	53.4	54.1
Lipid-lowering drugs	4.9	6.8	20.8	23.0	4.6	5.9	13.4	16.3
Osteoporosis therapy	1.8	2.2	8.4	7.9	2.0	2.6	10.1	10.4
Antidepressants	7.7	8.4	21.0	19.2	8.1	7.5	17.6	17.3
NSAID	14.6	19.0	36.6	36.9	19.5	24.4	35.2	37.8
Other analgesics	10.8	11.0	30.9	30.7	10.7	13.7	29.0	25.1
Opioids	4.9	7.3	16.1	16.1	4.6	7.2	13.0	14.0

*Antihypertensives, beta-blockers and/or diuretics.
COPD, chronic obstructive pulmonary disease; NSAID, non-steroidal antirheumatic drug.

more frequently in SLE compared with both controls (p<0.001; see table 2).

Sensitivity analyses

Data from 453 persons without additional autoimmune diagnoses were included in the first sensitivity analysis. The results showed no meaningful differences in the frequencies of comorbidity, drug prescriptions, hospitalisation and sick leave compared with the total sample (table 3).

In the second sensitivity analysis, only data from 312 persons with prescription of HCQ were included. Compared with the total cohort, persons with HCQ were younger (mean age 51.6 years), without a difference in gender distribution (87%). Persons with HCQ had slightly less comorbidity (mean Elixhauser 4.0 in the first year after diagnosis). The increase in concomitant diagnoses at the time of SLE diagnosis was comparable with the total cohort (table 3).

DISCUSSION

This claims data analysis on comorbidity and healthcare utilisation in individuals with SLE revealed a significant increase of comorbidity diagnoses already in the year of the first SLE diagnosis. These results exceeded

the frequencies in the control group without autoimmune disease, but were, in some aspects, comparable with patients with newly diagnosed diabetes. Increasing medical prescriptions, hospitalisation and days on sick leave were present in the first 2 years after SLE onset. Besides cardiovascular risk factors and renal disease, musculoskeletal and cerebrovascular disease affected a relevant number of persons at SLE onset.

Previous reports have indicated an increased risk of comorbidity in people with SLE,[1 13] which is already present in incident disease and affects mortality.[2] Our study confirms a higher comorbidity burden in comparison with matched general population cohorts.[1 2] However, the comparison with a matched cohort with incident diabetes shows a clear detection bias, leading to overestimation of the differences regarding comorbidity diagnoses with healthy controls. It can be assumed that numerous of these comorbidities were already present before SLE or diabetes was diagnosed and are only documented for the first time during the detailed diagnostic process.

Looking at the individual comorbidities, the proportion of depression (every third), osteoporosis (every fifth) and cerebrovascular disease (every tenth individual with SLE) needs to be particularly emphasised. Depression is one of the most frequent mental disorders affecting patients with SLE.[14] Almost one-third diagnosed with depression at SLE diagnosis point to the frequent mental affection. Increased rates of osteoporosis and fractures have been reported in SLE.[1 15] Whereas the regular use of glucocorticoids is likely to be responsible for osteoporosis in long-standing disease, it cannot be causal in incident disease. Pre-existing disease activity and premature menopause are more likely to be reasons for prevalent osteoporosis at SLE onset,[4 5] making early screening and risk assessment for fractures essential. It is also possible that the increase in osteoporosis codes for SLE may be due, in part, to heightened evaluation of osteoporosis risk after initiation of glucocorticoids or due to preventative osteoporosis therapies. Osteoarthritis was also more frequently diagnosed in SLE, but it also increased in the diabetes cohort. The increase is likely due to detection bias, as the joints of patients with SLE manifestations are regularly examined, whereas the joints in patients with diabetes are not necessarily examined as a priority. However, incorrect coding of joint manifestations of SLE cannot be ruled out.

Cerebrovascular disease is a known risk factor for mortality in SLE.[16] In the claims data, the diagnosis is more frequent compared with both control groups and this already applies to the year of SLE diagnosis.

Healthcare utilisation increases abruptly with SLE diagnosis. This can also be observed to a lesser extent in persons with diabetes. In particular, the increase in drug prescriptions, days on sick leave and hospital stays is substantial. While sick leave data are available, other measures of productivity loss such as presenteeism and impairment of unpaid work activities could not be captured in this analysis.

Besides SLE treatments including antimalarials, NSAIDs, corticosteroids and immunosuppressants, analgesics, opioids and drugs for treating comorbidities also contribute to an average prescription of 10 different drugs in the first and second year after diagnosis. US claims data show comparable medication use, frequent inpatient admissions and physician visits leading to high costs in the first postdiagnosis year.[17] Even if in Germany opioids are not prescribed as commonly as in the USA, where every third patient with SLE received opioids,[18] the frequency of prescription remains problematic. In addition, other analgesics, NSAIDs and antidepressants are also frequently prescribed.

Antimalarial prescription rates were comparatively low in this study, with 49% of the patients getting at least one prescription. We can compare this with the percentage receiving antimalarials in the German National Database of the collaborative arthritis centres. In 846 patients with a physician-reported SLE diagnosis in 2016, 64% received HCQ.[6] The National Database only covers patients in rheumatological care. In the incident SLE cohort in this manuscript, only 56% of the patients had contact with a rheumatologist. This might be a reason that antimalarial prescription rates are even lower in these patients.

The cardiovascular risk factors hypertension and hyperlipidaemia were more often present in persons with a diabetes mellitus diagnosis than in SLE, just as for prevalent SLE and diabetes mellitus patients among US Medicaid patients.[19] This could also be a result of detection bias; for example, lipid profiles were performed 33% more often in incident diabetes mellitus cases than in incident SLE. Lipid testing was also higher among patients with diabetes mellitus in the US Medicare data.[20] This could be problematic because another analysis of US Medicaid data shows that the incidence rate ratio for heart failure is comparable among patients with SLE and diabetes mellitus.[21]

The mean age and the proportion of women in this cohort are slightly higher compared with other incident lupus cohorts.[2 10] This can be explained by a higher proportion of women and a somewhat older population within the BARMER compared with the average of the statutorily insured population in Germany.

Claims data analyses have several limitations. The greatest limitation remains diagnostic uncertainty due to the lack of clinically validated diagnosis. Previous validation studies for the identification of SLE in administrative and claims databases had a positive predictive value in the range of 70%–90%.[22] To reduce potentially incorrect diagnostic codes, we included only individuals with continuous SLE diagnosis over 3 years. By adapting the validation algorithm of Schwarting *et al*,[10] we were able to classify 91% of the cases with a validity criterion. We further repeated the analyses only for cases with antimalarial therapy and without additional related autoimmune diagnoses that make SLE less likely. The high agreement between the analyses and the 50% proportion

of individuals with antimalarials suggests a good coverage of actual SLE cases.

A further limitation is that the diagnostic measures, for example, ANA tests, cannot be fully determined, as they are often billed at standard rates without specific numbers. In addition, diagnoses are often documented non-specifically, without organ manifestations being specifically reported. Therefore, no robust data on the prevalence of these manifestations can be generated from the data. The strengths of the study are the population-based sample, the high number of people with incident SLE and the possibility of collecting different matched control groups within the same population.

Regarding the generalisability of our data, the German health insurance data show a good estimate of the actual comorbidity diagnoses and prescription rates, which can be compared with data from other countries. Country-specific differences in healthcare delivery and uptake need to be taken into account. From a methodological point of view, ICD-10 codes are used ubiquitously and it is becoming increasingly important to interpret health insurance data correctly, as these are being used more and more for research purposes.

CONCLUSIONS

Comprehensive diagnostic measures after first manifestation of SLE reveal other concomitant diseases that are already present at the time of diagnosis, pointing towards the need for regular comorbidity assessment, already in incident disease. For comparisons between cohorts of patients with incident illness, the control group should be carefully selected. By considering different control groups, the influence of detection bias can at least be estimated to some extent.

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2.5. Nutzen von Krankenkassen-Abrechnungsdaten für die Identifikation von Personen mit rheumatoider Arthritis

In der Arbeit Komorbiditäten bei systemischem Lupus erythematodes wurden Daten der Barmer Krankenkasse genutzt, um Personen mit inzidenter Lupus-Diagnose zu identifizieren. Der systemische Lupus erythematodes ist wie in der Einleitung beschrieben eine der selteneren entzündlich-rheumatischen Erkrankungen. Es ist davon auszugehen, dass die ICD-10 Diagnose in den Abrechnungsdaten nur bei begründetem Verdacht vergeben wird. Anders ist dies bei der RA. Der geringe Anteil an rheumafaktor-positiven Personen an denen mit einer RA-Abrechnungsdiagnose in der Arbeit von Hense et al. (34) legt nahe, dass vor allem der ICD-10 Code M06 für seronegative RA auch vergeben wird, wenn keine gesicherte RA-Diagnose vorliegt, sondern möglicherweise eine andere entzündlich-rheumatische Erkrankung.

In der folgenden Arbeit wurde untersucht, wie gut die Abrechnungsdiagnosen mit selbstberichteten Diagnoseangaben für RA übereinstimmen und wie sich RA-Patient*innen in den Abrechnungsdaten am besten identifizieren lassen.

Der nachfolgende Text entspricht dem Abstrakt der Arbeit:

Callhoff J, Albrecht K, Marschall U, Strangfeld A, Hoffmann F. Identification of rheumatoid arthritis in German claims data using different algorithms: validation by cross-sectional patient-reported survey data. Pharmacoepidemiol Drug Saf. 2022.

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Abstract

Objective: To evaluate different algorithms for the identification of rheumatoid arthritis (RA) in claims data using patient-reported diagnosis as reference.

Methods: Within longitudinal data from a large German statutory health insurance, we selected a random sample of persons with ICD-10 code for RA (M05/M06) in ≥2 quarters in 2013. The sample was stratified for age, sex, and M05/M06. Persons were asked to confirm RA diagnosis (gold standard), which was linked to claims data given consent. Analyses were weighted to represent the total RA population of the database. Positive predictive values (PPVs) and discriminative properties were calculated for different algorithms: ICD-10 code only, additional examination of inflammatory markers, prescription of specific medication, rheumatologist appointment, or combination of these. **Results**: Of 6193 persons with a claims diagnosis of RA, 3184 responded (51%). Overall, PPV for the ICD-10 code was 81% (95% confidence interval 79%−83%) with 94% (92%−95%) for M05 and 76% (73%−79%) for M06. PPVs increased (with loss of case numbers) if inflammatory markers (82% [80%−84%]), rheumatology visits (85% [82%−87%]) or specific medication (89% [87%−91%]) had been used in addition. Specific medication had the best discriminative properties (diagnostic odds ratio of 3.0) among persons with RA diagnosis.

Conclusions: The ICD-10 codes M05 and (less optimal) M06 have high PPVs and are valuable to identify RA in German claims data. Depending on the respective research question, researchers should use different criteria for identification of RA.

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ORIGINAL ARTICLE

WILEY

Identification of rheumatoid arthritis in German claims data using different algorithms: Validation by cross-sectional patient-reported survey data

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Abstract

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Results: Of 6193 persons with a claims diagnosis of RA, 3184 responded (51%). Overall, PPV for the ICD-10 code was 81% (95% confidence interval 79%–83%) with 94% (92%–95%) for M05 and 76% (73%–79%) for M06. PPVs increased (with loss of case numbers) if inflammatory markers (82% [80%–84%]), rheumatology visits (85% [82%–87%]) or specific medication (89% [87%–91%]) had been used in addition. Specific medication had the best discriminative properties (diagnostic odds ratio of 3.0) among persons with RA diagnosis.

Conclusions: The ICD-10 codes M05 and (less optimal) M06 have high PPVs and are valuable to identify RA in German claims data. Depending on the respective research question, researchers should use different criteria for identification of RA.

KEYWORDS
claims data, diagnosis, electronic health records, ICD-10, validity

Key Points

- ICD-10 codes M05, M06 are valuable to identify rheumatoid arthritis (RA) in claims data.
- M05 has a higher positive predictive value compared to M06.

- However, as M06.9 is the most frequently used code for RA, selecting only M05 would result in a high loss of confirmed RA cases.
- We propose to select the criteria for identification depending on the research question, considering the trade-off between a relevant loss of case numbers and precision.
- If only definite RA cases are of interest, requiring a specific medication in addition to ICD-10 codes seems to be most suitable for identifying RA.

Plain Language Summary

Claims data are increasingly used for health services research into rheumatic diseases. For this purpose, it is important to reliably identify persons with rheumatic diseases. This study examined how well the claims diagnosis of rheumatoid arthritis is suitable as the sole criterion and whether additional data increase the probability that the diagnosis is true. For this purpose, a sample of persons with a claims diagnosis of RA was asked whether they really had RA and this was used as reference. The claims diagnosis for RA as a sole criterion was able to identify persons with RA in 80%. The correct identification was even higher if only people were classified as having RA if an anti-rheumatic drug had been prescribed or if anti-inflammatory markers had been examined. However, these additional requirements also resulted in individuals with confirmed RA not being included. Therefore, it depends on the research question which criteria are best suited to identify individuals with an RA diagnosis: if only definite RA cases are of interest, requiring a specific medication in addition to ICD-10 codes seems to be most suitable for identifying RA. However, if all persons with RA are to be included, for example, for questions of health care provision, then the claims diagnosis alone may be more advantageous.

1 | INTRODUCTION

Health services research focusing on the care of patients with rheumatoid arthritis (RA) relies on data that come from an unselected, representative population. While the German RA registries and cohort studies recruit patients from rheumatology care,[1–3] claims data from statutory health insurances could be a valuable source to recruit an unselected population. About 90% of German inhabitants are covered by statutory health insurance companies. Claims data store information about ICD-10 (International Classification of Diseases, 10th revision) codes, prescribed treatments like medication or physical therapy, the specialty of the visited physician, performed diagnostic procedures and more.

For studies using these data on questions regarding RA, researchers need to define a cohort carefully as different case definitions of RA strongly influence the results. Several studies investigated the prevalence of RA in Germany using claims data. They used a range of case definitions to obtain an RA diagnosis including the prerequisite of two outpatient or one inpatient ICD-codes, laboratory measures of inflammatory markers, specialized care by rheumatologists and specific treatments with disease modifying antirheumatic drugs (DMARDs) or glucocorticoids.[4–8] Depending on the algorithm used, the considered period, and the denominator used to calculate the prevalence, the prevalence of RA ranges between 0.6% and 1.4%.[4,5]

As physicians document ICD-codes in claims data for billing purposes, these diagnoses might not always meet the criteria for a clinical diagnosis. It is therefore important to validate case definitions against clinical diagnoses or other external data sources. While there is abundant research on the validity of case definitions of RA patients in US American and Canadian claims data sources,[9–14] we could not identify such a study with German claims data.

Therefore, the primary aim of this analysis was to compare different algorithms to identify patients with RA in German claims data and to assess their performance compared to the patient confirmation of RA diagnosis as a gold standard. A secondary aim was to compare algorithms with regard to their discriminative properties within the group of persons with a claims diagnosis of RA.

2 | METHODS

2.1 | Sample

We used data from the PROCLAIR project (Linking Patient-Reported Outcomes with Claims data for health services research In Rheumatology). The methods for this project have been described in detail elsewhere.[15] Briefly, data from a large German statutory health insurance with 6.6 million insurants aged 18–79 in 2013 were used to identify a stratified random sample of 6600 persons with an outpatient ICD-10 code for RA (M05, M06) in at least two quarters of 2013. The sample was stratified for age (18–49, 50–64 and 65–79 years), sex (male/

female) and diagnostic code (M05/M06), each stratum contained 550 persons. Ethical approval was obtained from the ethics committee of the Charité-Universitätsmedizin Berlin in March 2015 (EA1/051/15). This study was conducted in agreement with the declaration of Helsinki and its amendments. Persons gave written consent for the linkage of claims and survey data.

Persons in the sample were sent a questionnaire by their health insurance company in June 2015 that (among other things) asked them if they had RA. The phrasing of the question was "What does your attending physician call the disease you are suffering from?" with answer options, "chronic polyarthritis," "rheumatoid arthritis," "rheumatism of the joints," and "other (please specify)." The answer to this question was used as the gold standard for the diagnosis of RA.

2.2 | Data collection

Specific medication (glucocorticoids, conventional synthetic and biological disease-modifying antirheumatic drugs [cs and bDMARDs]), measurement of inflammatory markers (erythrocyte sedimentation rate, ESR or C-reactive protein, CRP) and rheumatologist visits were identified in the claims data of 2015 (the year of the survey). Drug prescriptions are based on the Anatomical Therapeutic Chemical (ATC) classification (see Appendix Table A1). The Elixhauser comorbidity score[16] was calculated.

2.3 | Statistical analysis

Characteristics of persons with self-reported RA diagnosis/no self-reported RA diagnosis and responders with non-responders were compared descriptively. The most frequently used ICD-10 codes and subcodes of RA were analyzed.

Follow up of ICD-10 code RA diagnosis was investigated from 2013 until 2020. For every year, we identified the proportion of persons who fulfilled the criterion of a claims diagnosis of RA in at least two quarters of the respective year. This analysis was performed to assess the persistence of RA diagnosis over time.

We assessed the positive predictive value (PPV) for several algorithms in addition to the ICD-10 codes M05/M06 in at least two quarters: ESR/CRP measurement, prescription of disease-specific drugs, rheumatologist visit, and all combinations of those. We considered the criteria as fulfilled if the measurement/prescription/contact was documented at least once during the entire year.

We calculated PPV based on the patient reported RA status from the survey in 2015 compared to the ICD-10 code in the claims data of 2013, which we used to draw the sample. PPVs were calculated for all possible strata and their combinations (women/men, Ages 18–49/50–64/65–79 years, ICD-10 code M05/M06). We weighted all analyses so that the values of all persons are representative of the total BARMER health insurance population with an M05/M06 diagnosis. This was done, because we used a stratified sample. The sample was stratified to ensure that we could also analyze underrepresented groups of RA patients (e.g., men younger than 50 years). The weights were calculated as the number of persons in the total BARMER population for that stratum divided by the number of respondents in this stratum. The weights are reported in Table A9.

As a sensitivity analysis, we calculated the PPV for all patients using the 2015 claims diagnosis of RA.

We performed the statistical analyses using the SURVEY procedures in SAS version 9.4.[17]

Additionally, we estimated the sensitivity and specificity, the Youden Index (Sensitivity + Specificity-1), the positive (LR+) and negative likelihood ratio (LR−) and the diagnostic odds ratio (LR+/LR−) for the considered algorithms to detect RA among those with two claims diagnoses of M05/M6. The LR+ shows the probability to be categorized as having RA given that a person actually has RA divided by the probability that the person is categorized as RA given that the person does not have RA. A higher LR+ indicates more favorable properties of the test. The LR− is the probability of someone being categorized as non-RA by the algorithm given they have RA divided by the probability of someone being categorized as non-RA given they do not have RA. The LR− ranges from 0 to 1 with lower values meaning more favorable properties.

The research paper was written in accordance with the Reporting of Studies Conducted Using Observational Routinely-Collected Data (RECORD) Guideline.[18]

3 | RESULTS

3.1 | Characteristics of the study population

Of the stratified sample of 6600 persons identified in the claims data from 2013, we contacted 6193 in 2015. The remaining persons had left the insurance company or were deceased. Of all contacted persons, 3184 (51%) responded to the questionnaire and 3140 gave their consent to combine survey and claims data. Responses were higher in persons with M05 diagnosis and among women, and ranged from 31% among men aged 18–49 years with an M06 diagnosis to 68% among women aged 18–49 with an M05 diagnosis.

A total of 2535 (81% of the responders) confirmed that they had RA, while 485 (19%) reported to have a different or no musculoskeletal condition (Figure 1).

Twenty persons did not answer the question if they had RA and were excluded from the analysis. The most frequently reported other diagnoses were osteoarthritis ($n = 90$), psoriatic arthritis ($n = 90$), ankylosing spondylitis/axial spondyloarthritis ($n = 73$), fibromyalgia ($n = 47$), polymyalgia rheumatica ($n = 30$), juvenile idiopathic arthritis ($n = 18$), and systemic lupus erythematosus ($n = 14$). For another 23 persons the answer was unclear, 18 persons reported to have no RA and did not report another diagnosis. The remaining 82 persons reported other conditions with a frequency of $n = 1$–12.

Table 1 shows the characteristics of the sample, comparing persons who confirmed the RA diagnosis, those who did not and those

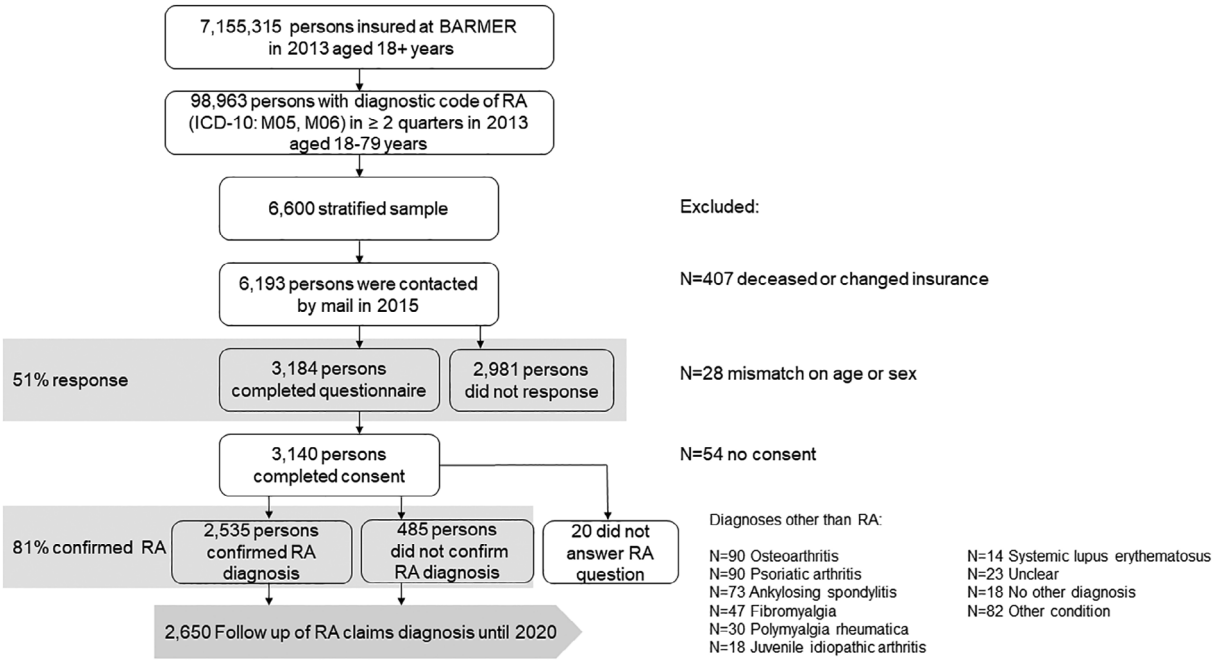

FIGURE 1 Flow Chart. ICD-10, International classification of diseases—10th revision; RA, rheumatoid arthritis; M05, ICD-10 code of seropositive RA; M06, ICD-10 code of seronegative RA.

TABLE 1 Characteristics

	Persons who confirmed RA-diagnosis	Persons who did not confirm RA-diagnosis	Survey non-responders (or no consent for linkage)
N (unweighted)	2535	485	3053
Effective sample size	1307	250	1606
Age, mean	65 (64; 66)	63 (61; 64)	63 (62; 63)
Women, %	80 (79; 82)	78 (74; 81)	79 (78; 81)
Seropositive RA (ICD-Code M05), %	31 (29; 33)	8.7 (6.6; 11)	21 (19; 22)
Specific medication (csDMARDs, bDMARDs, Glucocorticoids), %	57 (54; 60)	31 (25; 36)	30 (27; 32)
csDMARDs, %	48 (45; 51)	20 (16; 25)	26 (24; 28)
bDMARDs, %	15 (13; 16)	10 (7; 13)	7 (6; 8)
Glucocorticoids, %	49 (47; 52)	30 (24; 35)	34 (32; 37)
NSAIDs, %	53 (51; 56)	52 (46; 58)	46 (43; 48)
Elixhauser comorbidity index (0–31), mean	4.1 (4.0; 4.2)	4.1 (3.8; 4.4)	3.9 (3.8; 4.1)
ESR/CRP measurement, %	84 (82; 86)	76 (71; 81)	70 (68; 72)
Rheumatologist contact, %	55 (52; 57)	41 (36; 47)	30 (28; 32)

Note: Values are means or percentages as indicated with 95% confidence intervals. All results are weighted.
Abbreviations: bDMARD, biologic disease-modifying anti-rheumatic drug; csDMARD, conventional synthetic DMARD; NSAID, non-steroidal anti-inflammatory drug; RA, Rheumatoid arthritis.

who did not respond. The mean ages (65, 63, and 63 years), the Elixhauser comorbidity index (4.1, 4.1, and 3.9) and proportion of women (80%, 78%, and 79%) were comparable among the groups. Prescription rates for csDMARDs, bDMARDs and glucocorticoids were much higher among those who confirmed the diagnosis of RA compared to those who did not or those who did not respond.

3.2 | Specification of ICD-10 code for RA

Among the persons self-confirming RA diagnosis via survey, the diagnostic code M06.9 ("Rheumatoid arthritis, unspecified") was by far the most common one with 56% of all documented outpatient diagnoses in 2015. M05.9 ("Seropositive rheumatoid arthritis,

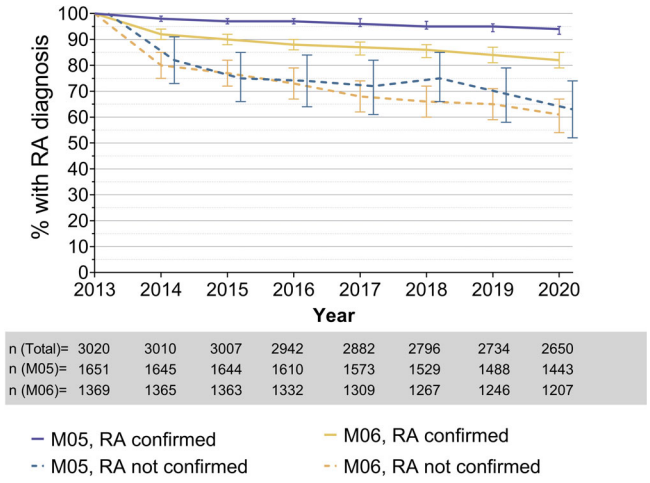

FIGURE 2 Consistency of ICD-10 code for RA. Proportion of persons who fulfilled the criterion of a claims diagnosis of RA in at least two quarters of the respective year, depending on M05/M06 status from 2013 and on self-confirmation of RA diagnosis in 2015. ICD-10, International classification of diseases—10th revision; RA, rheumatoid arthritis; M05, ICD-10 code of seropositive RA; M06, ICD-10 code of seronegative RA.

unspecified") and M05.8 ("Other seropositive rheumatoid arthritis") were the second most common diagnoses (each 15%). Among the persons not confirming an RA diagnosis, the most common codes were M06.9 (64%), M06.0 (12%, "Seronegative rheumatoid arthritis") and M05.9 (9%), see Appendix Table A2.

3.3 | Consistency of ICD-10 RA diagnosis 2013–2020

Figure 2 shows how many persons still had a coded RA diagnosis in the years from 2013 to 2020, stratified by seropositivity (2013 data) and patient confirmation of RA in 2015. A total of 94% (95% CI: 92%–95%) of those with an M05 diagnosis in 2013 who confirmed RA diagnosis in 2015 and 63% (95% CI: 52%–74%) of those who had the diagnosis in 2013 but did not confirm it in 2015 still had an RA diagnosis coded in 2020. In persons with an M06 diagnosis in 2013, 82% (95% CI: 79%–85%) of those who confirmed the diagnosis in 2015 and 61% (95% CI: 54%–67%) of those who did not confirm RA in 2015 still had RA claims codes in 2020.

3.4 | Positive predictive values for different case algorithms

Overall, the PPV was 81% (95% CI: 79%–83%) if no additional criterion other than two ICD-10 codes of M05/M06 in 2013 was applied. PPVs were markedly higher in persons with M05 (94%–96%) compared to persons with M06 diagnosis (76%–84%). PPVs increased if inflammatory markers (82 [95% CI: 80%–84%]), specific medication

TABLE 2 Positive predictive values (PPV) for confirmation of RA according to different selection algorithms

	No additional criterion	+ESR/CRP	+Medication	+Rheumatologist	+ESR/CRP Medication	+ESR/CRP Rheumatologist	+Medication Rheumatologist	+ESR/CRP Medication Rheumatologist
Number of persons with an ICD-10 code of M05 or M06 who fulfill the selection algorithm	3020	2610	1895	1824	1795	1791	1483	1463
PPVs for people with ICD-10 code M05 or M06, %	81 (79–83)	82 (80–84)	89 (87–91)	85 (82–87)	88 (86–91)	85 (82–87)	88 (85–90)	88 (85–90)
Number of persons with an ICD-10 code of M05 who fulfill the selection algorithm	1651	1528	1261	1200	1211	1187	1036	1026
PPVs for people with ICD-10 code M05, %	94 (92–95)	94 (93–96)	96 (95–98)	95 (94–97)	96 (95–98)	95 (94–97)	96 (94–97)	96 (94–98)
Number of persons with an ICD-10 code of M06 who fulfill the selection algorithm	1369	1082	634	624	584	604	447	437
PPVs for people with ICD-10 code M06, %	76 (73–79)	77 (74–80)	84 (80–87)	78 (75–82)	83 (80–87)	78 (74–82)	82 (77–86)	82 (77–86)

Note: Numbers are positive predictive values for a patient-reported diagnosis of RA with 95% confidence intervals in persons with ≥2 ICD-10 codes M05 or M06 (seropositive and seronegative Rheumatoid Arthritis). Columns present patients with selected ICD-10 codes fulfilling additional criteria of ≥1 ESR/CRP-measurement/prescription of specific medication/rheumatologist contact or combinations in 2015.
Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RA, rheumatoid arthritis.

TABLE 3 Discriminative properties of algorithms to identify rheumatoid arthritis in a population with M05/M06 diagnosis.

Algorithm in population with ICD-10 code M05/M06 in at least two quarters	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Youden-Index	Positive likelihood ratio	Negative likelihood ratio	Diagnostic odds ratio (LR+/LR−)
ESR/CRP	84 (82–86)	24 (19–29)	0.08	1.11	0.67	1.7
Specific Medication	57 (54–60)	69 (64–75)	0.26	1.84	0.62	3.0
Rheumatologist contact	55 (52–57)	59 (53–64)	0.14	1.34	0.76	1.8
ESR/CRP + Medication	53 (51–56)	71 (66–76)	0.24	1.83	0.66	2.8
ESR/CRP + Rheumatologist	53 (51–56)	59 (54–65)	0.12	1.29	0.80	1.6
Medication + Rheumatologist	42 (40–45)	75 (70–80)	0.17	1.68	0.77	2.2
ESR/CRP + Medication + Rheumatologist	42 (39; 44)	76 (71–80)	0.18	1.75	0.76	2.3

Note: Youden-Index (Sensitivity + Specificity-1).
Abbreviations: CI, Confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ICD-10, International classification of diseases—10th revision; LR, likelihood ratio; RA, rheumatoid arthritis.

(89 [95% CI: 87%–91%]) or rheumatology visits (85 [95% CI: 82%–87%]) had been used in addition (Table 2). A combination of any of these parameters did not further increase PPVs. Appendix Tables A3–A5 show PPVs according to seropositivity, age, and sex. PPVs were higher in females compared to males and in older compared to younger age groups. For all age, sex, and diagnosis groups, the algorithm including specific medication had the highest PPVs (68%–93% in M05/M06). Adding rheumatologist contact and/or ESR/CRP measurement to the algorithm did not lead to higher PPVs but decreased the case numbers (Appendix Tables A6–A8).

If, as performed in the sensitivity analysis, two ICD-10 codes of M05/M06 in 2015 (survey year) instead of 2013 (sampling year) were used, the PPV was 83% (95% CI: 81%–85%) for both M05/M06, 95% (95% CI: 94%–96%) for M05 only and 79% (95% CI: 76%–81%) for M06 only.

3.5 | Discriminative properties of the algorithms among persons with ICD-10 code for RA

Sensitivity of the assessed algorithms varied from 42%–84% with the highest sensitivity to detect RA resulting from ESR/CRP measurement. Specificity ranged from 24% to 76% with the highest value for the combination of ESR/CRP measurement, medication and rheumatologist visit, resulting in a Youden-Index of 0.18 (Table 3).

The algorithm with the best discriminative properties (the highest Youden-Index, the highest positive likelihood ratio, the lowest negative likelihood ratio and the highest diagnostic odds ratio) was specific medication (diagnostic odds ratio 3.0).

4 | DISCUSSION

The linkage of health insurance data with a patient survey enabled us to validate different algorithms for identifying persons with RA in German claims data. The analyses show that PPVs are moderate to high, depending on age, sex, and M05/M06 diagnosis, with M05 providing markedly higher PPVs. PPVs vary according to the used algorithm. The prerequisite of ESR/CRP measure, specific medication or rheumatology visits increase PPVs but this results in a loss of cases and in a decreased sensitivity. Our results allow choosing the best algorithm for different situations. If it is most important to cover a broad range of unselected RA patients, the algorithm with two ICD-10 codes in separate quarters of a year could be the best, as it has a PPV of 81% and includes as many persons as possible. If it were more important that all persons in the study have definite RA, it would be sensible to include only those with a prescription of specific medication. The data also indicate that the predictive values are not as good for certain subgroups, for example, for men aged 18 to 49 years. If this group is of particular interest, we suggest using a stricter algorithm than if older persons are the focus of the investigation. We further demonstrated that among the population with two claims diagnoses of RA in 1 year, the algorithm "at least one prescription of specific medication" was the one with the best performance with a sensitivity of 57% (95% CI: 54%–60%) and a specificity of 69% (95% CI: 64%–75%).

A systematic review by Chung et al. in 2013[9] revealed that PPVs for the detection of RA in administrative or claims data range from 34% to 97% depending on the population and the algorithm. Only US and Canadian sources were considered for this review. Factors found to increase PPVs were participation of a rheumatologist in patient care, prescription of a medication used to treat RA, requirement of a positive rheumatoid factor and the use of at least two ICD-codes of RA diagnoses. We incorporated these factors in our algorithms and also included the measurement of inflammatory markers as these can be regarded essential in the follow-up visits of RA patients. Our results are consistent with the US and Canadian sources and show a clear benefit in terms of PPV increase when specific medication, laboratory values or specialty care are assumed.

Other studies have examined other collectives and used other gold standards,[10–12,14,19] for example, a chart diagnosis or rheumatologist consultation/diagnosis, so that the results are not directly

comparable. PPVs also depend on the prevalence in the study population—the higher the prevalence, the higher the PPV (if sensitivity and specificity stay the same). Among the algorithms applied, the hospital discharge diagnosis is frequently found, but this only affects a fraction of persons because most of RA patients are treated as outpatients. Therefore, the discharge diagnosis (as a stand-alone criterion) seems not suitable for most research questions.

Data from Curtis et al.[13] show that M05 diagnoses can be used as a proxy to determine seropositivity with a sensitivity of 76% in US data from the American College of Rheumatology's Rheumatology Informatics System for Effectiveness and with a sensitivity of 73% in MarketScan data. The PPV to identify seropositive (vs. seronegative RA) was about 80% in the study by Curtis et al. In the PROCLAIR study, we had no means to evaluate the validity of the seropositivity as documented in the claims data. However, the differing PPVs for the RA diagnosis comparing M05 and M06 coded persons suggest that these subgroups are fundamentally different in terms of diagnostic certainty.

The analyses regarding the occurrence of RA diagnosis in the following years reveal that even with the broadest algorithm we used (an RA diagnosis in at least two quarters of a year) we missed 2%–4% of the seropositive and 8%–12% of the seronegative persons with self-confirmed RA in 2015. On the other hand, the RA claims often persist for several years, even if patients have not confirmed the diagnosis. Given that the majority of persons who did not confirm an RA diagnosis reported other inflammatory rheumatic diseases, it is plausible that physicians had an initial suspicion of an RA diagnosis and did not alter the documentation once another diagnosis was established. This seems to be independent of seropositivity and is also seen in other specialties. Longitudinal health insurance data on diabetes, colorectal cancer, and heart failure also show that diagnoses are not always conclusively continued.[20]

The results of the study also show that in German claims data, RA is predominantly coded non-specifically (M05.9, M06.9). This is also found in other German analyses, for example, regarding the coding of depression.[21] The predominance of M06 diagnoses is not reported from other countries. In data from Norway, two-thirds of RA cases are coded seropositive (M05) for inclusion criterion with two ICD-10 diagnoses.[21] This means that in German claims data, the proportion of incorrectly coded diagnoses may be higher and the proportion of seropositive RA is probably underestimated when only M05 cases are considered, limiting the generalizability of our data. Therefore, if we choose the inclusion criteria too widely, we end up with too many false positive cases but if we choose the inclusion too strictly and exclude the non-specific codes, as it was approached by Grellmann et al.,[8] we lose too many cases that would be true RA cases after all.

4.1 | Limitations and strengths

A strength of PROCLAIR is that we obtained the sample from the general German population covering also RA patients who are not in specialized rheumatologic care. Being able to identify also persons who do not see a rheumatologist is the foundation of being able to detect possible deficiencies in healthcare provision. BARMER is one of the largest health insurance companies in Germany and covers around 12% of the persons that have a statutory health insurance. Deviations in the structure of the insured persons (BARMER has a slightly higher proportion of elderly women compared to other insurance companies[22]) can be taken into account through standardization.[4] Within this large sample drawn, we were able to obtain age- and sex-specific results with a sufficient number of cases in the individual strata. The survey part of our study had a response of 51%, which is high compared to similar studies.[23,24] Another strength of the study is the longitudinal follow-up of ICD-10 codes.

Limitations include differences between survey responders and non-responders, which may occur due to a different willingness to respond to the survey and link the data in persons who actually have RA compared to those who do not. One observed difference is that survey non-responders were treated with DMARDs less frequently compared to responders. An evaluation from PROCLAIR on persons with an osteoarthritis or an axSpA-diagnosis had already revealed that survey responsiveness differed according to age and sex. Moreover, survey responders visited specialists and received health care interventions, such as vaccinations or prescriptions for specific drugs and physical therapy, more frequently than non-responders .[25] While those differences between survey responders and non-responders probably affect the PPVs, there is no reason to believe that they would change the ranking of the most suitable algorithm to identify RA patients in German claims data.

Our algorithms rely on ICD-10 codes recorded by physicians and additional information available in claims data. Yet, we lack data on classification criteria for RA, as well as data on clinical investigations. As we have not contacted any persons without two diagnostic codes of RA in the claims data, we cannot assess sensitivity and specificity for the different algorithms to identify RA in claims data for the general population.

In PROCLAIR, we used patient reported diagnoses as a gold standard instead. Given that the sample population was randomly selected from all areas of Germany and included persons who are not in rheumatologist care, it would not have been feasible to contact all treating physicians and ask them to confirm the existence of a clinical RA diagnosis. We decided to use the patient-reported diagnosis as a proxy for the clinical diagnosis. This is a limitation of our study. Guillemin et al.[26] concluded that self-reported diagnosis is the single most useful item to identify patients with a clinical diagnosis of RA, given that there is no data from the treating physician available directly.

5 | CONCLUSIONS

The ICD-10 codes M05 and (less optimal) M06 have high PPVs and are therefore feasible to identify persons with RA in German claims data. Depending on the research question, additional requirements can lead to a more precisely defined cohort at the cost of lower case numbers. We found the additional prerequisite of a prescription of specific medication to be the most useful algorithm considering this trade-off.

AUTHOR CONTRIBUTIONS

Johanna Callhoff had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Johanna Callhoff, Katinka Albrecht, Falk Hoffmann. Acquisition, analysis, or interpretation of data: Johanna Callhoff, Katinka Albrecht, Ursula Marschall, Anja Strangfeld, Falk Hoffmann. Drafting of the manuscript: Johanna Callhoff, Katinka Albrecht, Falk Hoffmann. Critical revision of the manuscript and approval of the manuscript: Johanna Callhoff, Katinka Albrecht, Ursula Marschall, Anja Strangfeld, Falk Hoffmann.

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CONFLICT OF INTEREST

Johanna Callhoff, Katinka Albrecht, Falk Hoffmann, Anja Strangfeld: None declared. Ursula Marschall is an employee of the BARMER. There were no financial and personal relationships with other people or organizations that could inappropriately influence (bias) this work.

DATA AVAILABILITY STATEMENT

The datasets supporting the conclusions of this article are included within the article and its additional file.

ETHICS STATEMENT

Obtained from the ethics committee of the Charité-Universitätsmedizin Berlin in March 2015 (EA1/051/15). The persons gave their written informed consent according to the Declaration of Helsinki.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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3. Diskussion

In den vorliegenden Arbeiten wurde auf verschiedene Herausforderungen der rheumatologischen Versorgung und der epidemiologischen Forschung in der Rheumatologie eingegangen. Insbesondere die Diagnose entzündlich-rheumatischer Erkrankungen, aber auch die ihrer Komorbiditäten und Organmanifestationen spielen eine große Rolle für die adäquate Versorgung. Für die epidemiologische Forschung und Versorgungsforschung ist es sehr hilfreich, Personen mit RA zuverlässig in Sekundärdaten identifizieren zu können. Dadurch wird eine noch relativ neue Datenquelle erschlossen, die Möglichkeiten eröffnet, die bisher wenig untersuchte Population der fachärztlich nicht betreuten Personen zu untersuchen. Die zentralen Ergebnisse und Implikationen für die epidemiologische Forschung und Patientenversorgung entzündlich-rheumatischer Erkrankungen der Arbeiten aus Kapitel 2 werden in diesem Kapitel diskutiert.

3.1. Große Diagnoseverzögerung bei axialer Spondyloarthritis in Deutschland

Leider zeigen Daten aus der rheumatologischen Versorgung in Deutschland, dass das Ziel einer frühen Behandlung oft nicht erreicht wird. Aus Daten der Kerndokumentation der regionalen kooperativen Rheumazentren (9) geht hervor, dass nur 49% der RA-Patient*innen in 2020 innerhalb von höchstens 3 Monaten eine Vorstellung in der Rheumatologie hatten. Bei der axSpA hatten nur 44% eine Vorstellung innerhalb des ersten Jahres nach Symptombeginn, der Median lag sogar bei 18 Monaten (9) (Zeitraum der Erstvorstellung war hier 2016 bis 2020).

In der Arbeit Zeitverzögerung bis zur Diagnosestellung axialer Spondyloarthritis wurde auf Basis von 1677 patientenberichteten Angaben aus dem Forschungsprojekt PROCLAIR (Linking patient-reported outcomes with claims data for health services research in rheumatology (35)) untersucht, wie groß die Diagnoseverzögerung bei gesetzlich Versicherten der Barmer Krankenkasse im Mittel ist. Im Median mussten Patient*innen mit axSpA 2,3 Jahre warten, bis sie eine Diagnose erhalten haben. Dies ist etwas niedriger als die Zahlen im internationalen Vergleich, wie Hay et al. in einem systematischen

Review (36) gezeigt haben. Hier war die Spannweite für die mediane Diagnoseverzögerung in 25 Studien 0,67 bis 8 Jahre. In 40% der Studien dieses Reviews war der Median 2,3 oder kleiner.

Redeker et al. stellten auch dar, dass sich die mediane Dauer bis zur Diagnose in den Zeiträumen 1996-2005 und 2006 bis 2015 kaum unterschied (Median im Zeitraum 1996- 2005: 2,6 Jahre, im Zeitraum 2006-2015: 2,7 Jahre). In der Kerndokumentation (9) war die mediane Dauer von Symptombeginn bis zur Erstvorstellung in der Rheumatologie im Zeitraum 2001-2005 3,5 Jahre, in 2006-2010 0,8 Jahre, in 2011-2015 1,7 Jahre und in 2016-2020 1,5 Jahre. Auch hier zeigt sich, dass es keine konsistente Verbesserung der Zeit bis zur Erstvorstellung in den Jahren seit 2006 gegeben hat.

Es wurden verschiedene Merkmale untersucht, die bei der Diagnose einer axSpA eine Rolle spielen: Psoriasis, chronisch-entzündliche Darmerkrankungen (CED), Uveitis, HLA-B27 Positivität und auch das Geschlecht. Psoriasis (Schuppenflechte), CED und Uveitis werden auch als extra-artikuläre Manifestationen der axSpA bezeichnet. Sie werden neben dem Hauptsymptom- entzündlichem Rückenschmerz- in den Klassifikationskriterien der axSpA der ASAS (27) (Assessment of SpondyloArthritis international Society) verwendet. Es ist zunächst überraschend, dass sich in der Arbeit von Redeker et al. (37) bezüglich des Vorhandenseins dieser extra-artikulären Manifestationen kein Unterschied in der Dauer von Symptombeginn bis zur Diagnose gezeigt hat. So hatten 9,6% von denjenigen mit einer Diagnoseverzögerung von weniger als 2,3 Jahren eine CED und 8,5% von denen mit Diagnoseverzögerung von 2,3 Jahren oder mehr (p=0,45). Auch bei Uveitis (26,4% vs. 29,1%, p=0,23) und Psoriasis (13,9% vs. 16,2%, p=0,20) hab es keinen deutlichen Unterschied zwischen den Gruppen. Dazu muss man aber bedenken, dass die Befragten angaben, ob sie jemals eine der extra-artikulären Manifestationen hatten- es ist also möglich, dass diese erst nach Diagnosestellung aufgetreten ist bzw. sind.

Anders war dies bei der HLA-B27 Positivität. Dies ist ein genetischer Marker, der stark mit dem Vorhandensein einer axSpA assoziiert ist. In einer Studie im Vereinigten Königreich von 1996 hatten 94% der 284 AS-Patient*innen das HLA-B27 Allel, aber nur 9,5% der 5926 Kontrollen. In 2022

veröffentlichte Daten von Boel et al. (38) zeigen, dass die Assoziation von HLA-B27 Positivität mit positiver Familienanamnese für axSpA in Asien, Europa und Nordamerika und Lateinamerika besteht, nicht aber im mittleren Osten und Nordafrika. Dieser genetische Marker kann also nicht alleine zur Diagnose verwendet werden, aber ein Verdacht kann verstärkt werden, wenn jemand europäischer Herkunft positiv auf diesen genetischen Marker getestet wurde. So war in PROCLAIR (37) im Regressionsmodell die Zeit bis zur Diagnose um über 3 Jahre kürzer bei positivem HLA-B27 Test als bei negativem Test.

In der PROCLAIR-Befragung war die Diagnoseverzögerung bei Frauen deutlich größer (1,6 Jahre länger im Vergleich zu Männern, 95% KI 0,9-2,3). Im Review von Hay et al. (36), das die Diagnoseverzögerung bei Frauen im Vergleich zu Männern in 20 Studien vergleicht, wurde für das Geschlecht kein Einfluss auf die Diagnoseverzögerung deutlich. Ob dieser Unterschied also spezifisch für die deutsche Versorgungslandschaft ist oder ob der Unterschied in PROCLAIR zufällig entstanden ist, bleibt offen.

Eine entscheidende Limitation der PROCLAIR-Befragung zur Diagnoseverzögerung ist der mögliche Erinnerungsbias bei der Erhebung der Diagnoseverzögerung. Eine Erfassung der Dauer von Symptombeginn bis zur Diagnose einer Erkrankung, die vor der Diagnose geschieht erscheint allgemein kaum möglich. Doch zumindest zum Zeitpunkt der Diagnosestellung kann dieses Intervall erhoben werden. In PROCLAIR sind seit Diagnosestellung im Mittel 20 Jahre vergangen, wodurch ein Recall-Bias wahrscheinlich ist.

3.1.1. Projekte in Deutschland zur Verkürzung der Zeit bis zur Diagnose einer entzündlich-rheumatischen Erkrankung

Es gibt verschiedene Projekte und Initiativen in Deutschland mit dem Ziel, die Zeit von Symptombeginn bis zur Diagnose bei entzündlich-rheumatischen Erkrankungen zu verkürzen. Das Rheuma-Netzwerk ADAPTHERA („risikoadaptierte Rheumatherapie“) in Rheinland-Pfalz (39) startete 2012 mit seiner Pilotphase, um die Zeit bis zur Diagnose einer RA zu verkürzen. Dieses Ziel konnte erreicht werden: So

dauerte es im Mittel 24 Tage von der Vorstellung in der hausärztlichen Praxis bis zur Diagnosestellung durch eine*n Rheumatolog*in. Zentral dafür ist eine Koordinierungsstelle, bei der die Hausärzt*innen für Personen mit Verdacht auf eine RA melden können. Bei dieser werden dann zentral möglichst zeitnah Termine zur fachärztlichen Abklärung der rheumatischen Erkrankung vergeben. Aufbauend auf dem Netzwerk von ADAPTHERA wurde das Innovationsfonds geförderte Projekt Rheuma-VOR gestartet. Hier wurde in Rheinland-Pfalz, Niedersachsen, dem Saarland und Berlin evaluiert, wie viel schneller im Durchschnitt eine RA, axSpA oder PsA diagnostiziert wird, wenn die Diagnose über die im Rahmen von Rheuma-VOR koordinierte Terminvergabe abgeklärt wird (40). Benesova et al. (41) haben in einem Überblicksartikel in 2019 einen umfassenden Überblick über Früherkennungs-Sprechstunden und koordinierte Früherkennungsprojekte gegeben. Ein gemeinsames Merkmal aller dieser Projekte uns Sprechstunden ist die gezielte Terminvergabe. Personen mit Verdacht auf eine entzündlich-rheumatische Erkrankung oder ihr behandelnder Hausarzt füllen einen kurzen Fragebogen aus/beantworten telefonisch Fragen. Darauf basierend gibt es eine Einschätzung, ob eine entzündlich-rheumatische Erkrankung wahrscheinlich ist oder nicht. Wenn genügend typische Anzeichen für eine entzündlich-rheumatische Erkrankung vorliegen, wird ein Termin zur Abklärung innerhalb eines kurzen Zeitraums (möglichst weniger Wochen) vergeben, sonst wird ein Termin mit einer größeren Wartezeit vergeben. Dies soll ermöglichen, dass für möglichst viele Patient*innen mit entzündlichen Erkrankungen das „Window of opportunity“ genutzt werden kann. Im RhePort-Netzwerk (42) passiert diese Triage über ein internetbasiertes Priorisierungstool. Für die Priorisierung entscheidend sind die Fragen bzw. Angaben, die im Priorisierungsalgorithmus hinterlegt sind. Während bei der Abklärung auf eine mögliche RA die Anzahl der geschwollenen und schmerzhaften Gelenke eine wichtige Rolle spielt, ist das Leitsymptom der axSpA der entzündliche Rückenschmerz.

In der Studie DIVERS (Diagnostic Accuracy of Inflammatory Back pain study) (43) (dargestellt in Kriterien entzündlichen Rückenschmerzes bei der Diagnose einer axialen Spondyloarthritis) wurden verschiedene Kriterien zur Erkennung entzündlichen Rückenschmerzes anhand eines kurzen Fragebogens auf ihre diagnostische Güte hin untersucht. Es wurde außerdem untersucht, ob diese von

Hausärzt*innen gleich gut wie von Patient*innen oder Rheumatolog*innen erhoben werden können. Ein weiteres Ziel von DIVERS war festzustellen, welchen Wert der entzündliche Rückenschmerz in der Diagnostik der axSpA spielt. Von 461 Personen mit chronischem Rückenschmerz, die zur rheumatologischen Abklärung überwiesen worden sind, hatten 66% entzündlichen Rückenschmerz. Goldstandard der Beurteilung war die Einschätzung eines verblindeten Rheumatologen.

Es wurden in DIVERS drei Kriterien-Sets für entzündlichen Rückenschmerz getestet: Die Calin-Kriterien, die Berlin-Kriterien und die ASAS-Kriterien (27). Diese wurden von drei Personengruppen erhoben: Dem behandelnden Rheumatologen, einem für die Diagnose verblindeten Rheumatologen und den Patient*innen. Es zeigte sich, dass die diagnostische Güte der Kriterien gemessen an positivem Likelihood Ratio und negativem Likelihood Ratio nicht relevant unterschieden. Daraus kann man schließen, dass alle Kriterien-Sets gleichermaßen verwendet werden können.

Die diagnostische Güte der patientenberichteten Angaben unterschied sich zudem kaum von der diagnostischen Güte der verblindeten Rheumatolog*innen. Das zeigt, dass es legitim ist, patientenberichtete Angaben zu verwenden, wenn es darum geht zu entscheiden, welche Personen möglichst dringlich einen Termin zur Abklärung einer axSpA-Diagnose erhalten sollten.

Gerade Projekte wie Rheuma-VOR und RhePort konnten von diesen Ergebnissen DIVERS profitieren. Aufbauend auf den Ergebnissen aus DIVERS wurde an der Charité- Universitätsmedizin Berlin die OPTIREF-Studie (44) durchgeführt (Optimal Referral Strategy for Early Diagnosis of Axial Spondyloarthritis). Hier wurde verglichen, ob sich Patient*innen die anhand der erfüllten Berlin-Kriterien zur rheumatologischen Abklärung überwiesen worden sind von solchen unterschieden, die bei einem online-Fragebogen die Überweisungskriterien erfüllten. Die Studie hat gezeigt, dass der online-Fragebogen eine sinnvolle Ergänzung zu bestehenden Diagnosepfaden sein kann- insbesondere, weil damit auch ein größeres Bewusstsein für die Erkrankung geschaffen werden kann. Hier ist es auch möglich, die Grenzwerte dafür, wann jemand einen dringlichen Termin zur Abklärung erhält flexibel anzupassen, auf Basis aktueller Forschung neue Fragen hinzuzunehmen oder technisch

komplexere Methoden der Selektion- wie z.B. maschinelles Lernen einzusetzen. Zur Erkennung von entzündlich-rheumatischen Erkrankungen allgemein gab es hier schon erhebliche Fortschritte. Durch den Einsatz von maschinellem Lernen konnte eine höhere diagnostische Genauigkeit erzielt werden als mit dem bisherigen RhePort-Algorithmus (45). Bei einer prä-definierten Sensitivität von 90% wurde die Spezifität von 17% (bisheriger Algorithmus) auf 33% erhöht.

Neben den Bemühungen, mit den bestehenden Ressourcen eine optimale Früherkennung zu erzielen ist es unabdingbar, dass die Kapazitäten in der rheumatologischen Versorgung in Deutschland größer werden.

3.1.2. Internationale Perspektive und Ausblick

Die frühe Erkennung entzündlich-rheumatischer Erkrankungen, insbesondere der axSpA, ist ein weltweites Problem. Auch international gibt es Bemühungen, valide Screening-Tools zu entwickeln (46), um Patient*innen früh an die entsprechenden Fachärzt*innen überweisen zu können, falls nötig. Bei der Evaluation einer Überweisungsstrategie (47) (bei Erfüllung von mindestens zwei der folgenden Kriterien sollte eine Überweisung erfolgen: 1. Erfüllung der ASAS-Kriterien für entzündlichen Rückenschmerz 2. Positive Familienanamnese für Spondyloarthritis 3. Gutes Ansprechen auf NSAR 4. entzündlicher Rückenschmerz länger als 5 Jahre) gab es keinen Unterschied in der durch entzündlichen Rückenschmerz verursachten Behinderung 4 Monate nach Überweisung. Verglichen wurde eine Gruppe, die bei Erfüllung der Kriterien in die Rheumatologie überwiesen wurde und eine Gruppe mit Standardbehandlung. Es könnte sein, dass 4 Monate ein zu kurzer Zeitraum gewesen sind, um hier klinisch relevante Unterschiede zwischen den Gruppen festzustellen. Dennoch tragen Studien wie diese (47) und ähnliche (44) auch dazu bei, die Aufmerksamkeit in der Bevölkerung und bei Allgemeinmediziner*innen für Krankheiten wie die axSpA zu erhöhen und können potentiell positive Effekte bewirken.

Mangelndes Wissen bei Allgemeinmediziner*innen kann dazu beitragen, dass typische Symptome nicht erkannt werden und zu einer sehr späten Diagnose beitragen. In einer qualitativen Studie aus

den USA mit 10 befragten, männlichen Allgemeinmedizinern dachten alle Befragten, dass AS fast ausschließlich bei Männern vorkäme (48). Gezielte Fortbildung von Allgemeinmediziner*innen sowie gute Kriterien zur Zuweisung zur Rheumatologie kann helfen, um die Situation für Rheumakranke zu verbessern. Aus Sicht der Allgemeinmediziner*innen selbst würde eine größere Aufmerksamkeit für die Erkrankung und ein gutes Screening-Tool dazu beitragen, einer Diagnoseverzögerung entgegenzuwirken (49). Insbesondere zur Steuerung des Zugangs zu Frühsprechstunden wird maschinelles Lernen in Zukunft bei Diagnosepfaden der axSpA und anderer entzündlich-rheumatischer Erkrankungen eine Rolle spielen.

3.2. Herausforderungen bei der Nutzung von GKV-Abrechnungsdaten in der Forschung mit entzündlich-rheumatischen Erkrankungen

3.2.1. Identifikation von Personen in fachärztlicher Behandlung

Während für Untersuchungen zur Diagnoseverzögerung zwingend notwendig patientenberichtete Angaben benötigt werden, da sich der Symptombeginn anders nicht feststellen lässt, gibt es andere Fragestellungen, die sich hervorragend mit Sekundärdaten wie GKV-Abrechnungsdaten beantworten lassen. Insbesondere Fragestellungen zu Medikamentengebrauch und Komorbiditäten können gut mit Abrechnungsdaten der gesetzlichen Krankenkassen untersucht werden. Große Beobachtungsstudien in der Rheumatologie wie die Kerndokumentation der regionalen kooperativen Rheumazentren (50), das Biologika-Register RABBIT (51) (Rheumatoide Arthritis: Beobachtung der Biologika-Therapie) und RABBIT-SPA rekrutieren ihre Teilnehmenden ausschließlich über rheumatologische Einrichtungen. Dies geschieht aus praktischen Gründen: Entzündlich-rheumatische Erkrankungen sind so selten, dass Allgemeinmediziner*innen in der hausärztlichen Versorgung nur Kontakt zu wenigen Betroffenen haben. Eine Befragung von Versicherten der Barmer mit ICD-10 Diagnose für RA (ICD-10-GM Code M05 bzw. M06) (5) in 2015 (Projekt PROCLAIR (35)) hat gezeigt, dass sich zum Zeitpunkt der Befragung 68 % der RA-Patient*innen in rheumatologischer Betreuung befanden. Die Angaben zu Schmerzen, Funktionsfähigkeit und betroffenen Gelenken unterschied sich nicht relevant zwischen der rheumatologisch betreuten Gruppe und der nicht fachärztlich betreuten Gruppe. Die medikamentöse

Versorgung dieser beiden Gruppen war allerdings stark unterschiedlich- in der nicht rheumatologisch betreuten Gruppe erhielten viel weniger Personen DMARDs. Das kann als ein Hinweis auf Unterversorgung der nicht fachärztlich betreuten Gruppe verstanden werden. Dieses Beispiel zeigt, dass ein verzerrtes Bild von der rheumatologischen Versorgung in Deutschland entsteht, wenn nur Personen in fachärztlicher Betreuung untersucht werden.

In PROCLAIR wurden die Betroffenen direkt gefragt, ob sie sich in rheumatologischer Behandlung befinden. Bei den meisten Analysen mit GKV-Abrechnungsdaten stehen keine verknüpften Befragungsdaten zur Verfügung. In diesem Fall muss die Frage, ob fachärztliche Betreuung besteht direkt aus den Abrechnungsdaten abgeleitet werden. Dies kann im Datensatz der Barmer über eine anonymisierte lebenslange Arztnummer (LANR) erfolgen: In den letzten zwei Ziffern der LANR ist der sog. Fachgruppenschlüssel codiert, über den sich internistische Rheumatolog*innen (Fachgruppenschlüssel 31), orthopädische Rheumatolog*innen (Fachgruppenschlüssel 12) und auch Orthopäd*innen (Fachgruppenschlüssel 10) identifizieren lassen. Diese Zuordnung ist allerdings nur zum Teil möglich: Es gibt zum einen internistische Rheumatolog*innen, die hausärztlich niedergelassen sind und somit den Fachgruppenschlüssel 03 für „Internist (Hausarzt)“ tragen. Andererseits findet ein Teil der ambulanten rheumatologischen Versorgung über Klinik-Ambulanzen statt. Hier lässt sich in den Daten nicht erkennen, welche Facharztgruppen an der Versorgung beteiligt sind. Der Anteil an rheumatologisch versorgten Personen wird anhand von Abrechnungsdaten also eher unterschätzt.

3.2.2. Validität von Diagnosen

In der Arbeit Nutzen von Krankenkassen-Abrechnungsdaten für die Identifikation von Personen mit rheumatoider Arthritis wurde gezeigt, dass sich Personen mit RA relativ gut in Abrechnungsdaten der Barmer identifizieren lassen. Der positive prädiktive Wert von mindestens einem ICD-10-Code für RA (M05, M06) in zwei verschiedenen Quartalen eines Jahres zur Identifikation von Personen mit RA lag bei 81% (95% Konfidenzintervall (KI) 79% - 83%)(52). Möchte man eine Kohorte definieren, in der noch sicherer vorwiegend „echte“ RA-Fälle befinden, kann man die Verschreibung spezifischer Medikation als zusätzliches Kriterium anwenden und erhält dann sogar einen positiven prädiktiven Wert von 89 %.

Je nach Fragestellung können sich die Forschenden entscheiden, welche Kohortendefinition besser geeignet ist.

Es wurde gezeigt, dass insbesondere der ICD-Code M06 für seronegative RA weniger spezifisch zur Identifikation von RA-Patient*innen ist (positiver prädiktiver Wert 94 %, 95 % KI 92 %-95 %) als der Code M05 für seropositive RA (positiver prädiktiver Wert 76 %, 95 % KI 73 %-79 %). Klare Limitation dieser Studie ist, dass keine klinisch validierten Diagnosen vorhanden waren, sondern die Patientenangabe als Goldstandard verwendet wurde. Optimal wäre es, Daten klinischer Kohortenstudien wie der Kerndokumentation oder des Biologika-Registers RABBIT mit Abrechnungsdaten der Krankenkassen zu verknüpfen. Aufgrund des hohen Aufwands gibt es solche verknüpften Daten in Deutschland bisher nur selten, z.B. im Rahmen der SHIP-Kohorte (53).

In den letzten Jahren wurden vermehrt Analysen zu RA-Betroffenen auf Basis von Abrechnungsdaten veröffentlicht, bei denen die Kohorte ausschließlich basierend auf ICD-10-Diagnosen definiert worden ist (54-56). Es ist anzunehmen, dass in diesen Kohorten insbesondere bei denjenigen mit M06-Diagnose viele befinden, die nicht an RA erkrankt sind. Oft liegen mehrere Abrechnungsdiagnosen von verschiedenen entzündlich-rheumatischen Erkrankung vor. In der Analyse von Leipe et al. (56) haben z.B. 33,5 % derjenigen mit Psoriasis-Arthritis-Diagnose auch eine Diagnose einer seronegativen RA. Bei einem großen Teil dieser Personen könnte es sich um Fehlcodierungen handeln, denn RA und PsA haben zwar überlappende Symptome, es wird typischerweise dann aber nur eine der beiden Diagnosen gestellt (57). Dies illustriert anschaulich eine der Limitationen von Abrechnungsdaten: Sie werden primär für die Abrechnung von Leistungen erhoben, nicht für die Forschung.

Dem gegenüber steht die größte Stärke dieser Daten: Alle Medikamente, Operationen und Verordnungen für Hilfs- und Heilmittel (dazu zählen physikalische Therapie und Ergotherapie), die im ambulanten Bereich verordnet werden sind dort dokumentiert. Gelingt es also, eine Kohorte mit ausreichender Trennschärfe zu definieren, können Fragestellungen zu Ressourcenverbräuchen und Arzneimittelverordnung sehr gut untersucht werden.

3.2.3. Detektionsbias bei der Dokumentation von Komorbiditäten

Eine weitere Herausforderung im Umgang mit Abrechnungsdaten hat sich in der Arbeit Komorbiditäten bei systemischem Lupus erythematodes gezeigt. Hier wurde untersucht, wie sich die Häufigkeit ausgewählter Komorbiditäten bei Patient*innen mit inzidentem systemischen Lupus erythematodes im Jahr der Lupus-Diagnose und im Jahr danach verändert. Im Vergleich mit alters- und geschlechtsgematchten Kontrollen ohne Autoimmunerkrankung zeigte sich, dass im Jahr der Lupus-Diagnose der Anteil an Personen mit Hypertonie, Hyperlipidämie, Depression, Osteoporose, Arthrose und kardiovaskulären Erkrankungen deutlich stieg. Dies war bei Kontrollen mit inzidentem Diabetes Mellitus in ähnlichem Umfang der Fall, was auf einen Detektionsbias hindeutet. Sowohl beim SLE als auch bei Diabetes Mellitus werden neu Diagnostizierte umfassend und gründlich auf kardiovaskuläre, renale und neurologische Erkrankungen hin untersucht. So kommt es in den Abrechnungsdaten zu einem sprunghaften Anstieg des Anteils an Personen mit Hypertonie, Hyperlipidämie, Depression und weiteren Erkrankungen.

Der dadurch entstehende Bias ist ein weiteres grundsätzliches Problem von Abrechnungsdaten: Es sind nur diagnostizierte Komorbiditäten in den Daten abgebildet. Diesen Bias gibt es gleichermaßen bei Beobachtungsstudien wie der Kerndokumentation oder im Biologika-Register RABBIT, in denen der Versorgungsalltag abgebildet wird. Die Häufigkeit z.B. der Osteoporose für SLE-Patient*innen in der Kerndokumentation (9 % SLE-Patient*innen mit Osteoporose bei mittlerer Krankheitsdauer von 17 Jahren, Daten von 2020 (9)) ist deutlich niedriger als die Häufigkeit in Abrechnungsdaten (20 % SLE-Patient*innen mit Osteoporose im Jahr der inzidenten SLE-Diagnose, Daten von 2016). Dies ist ein klarer Hinweis darauf, dass Komorbiditäten in der Kerndokumentation deutlich untererfasst sind. Es gibt also sowohl in Primärerhebungen als auch in Sekundärdaten Hinweise auf Untererfassung von Begleiterkrankungen. Diese passiert aber aus verschiedenen Gründen: Während in den Abrechnungsdaten nicht vorhandene Diagnosen wahrscheinlich nicht ärztlich gestellt worden sind, könnte es bei der Kerndokumentation sein, dass sie dem Facharzt/der Fachärztin nicht bekannt sind, wohl aber der Hausärztin oder dem Hausarzt.

Wegen dieses starken Detektionsbias konnte die Frage, wie schnell nach Beginn der SLE-Erkrankung ausgewählte Komorbiditäten entstehen, mit den GKV-Abrechnungsdaten nicht beantwortet werden. In Deutschland gibt es zwei weitere große Datenquellen, die SLE Betroffene beinhalten. Zum einen die LuLa-Kohorte (58, 59), bei der vorwiegend patientenberichtete Angaben erfasst werden. Hier wurden in 2012 von 585 Betroffenen Angaben zu betroffenen Organsystemen und der Dauer der Diagnose erfasst. Die mittlere Krankheitsdauer lag bei 18 Jahren, sodass anhand dieser Daten schwer untersucht werden kann, wie sich die SLE-Erkrankung im zeitlichen Verlauf auf betroffene Organe ausgewirkt hat.

Weiterhin gibt es die Kerndokumentation (50), bei der in 2020 Daten von 829 Personen mit SLE erfasst wurden. Allerdings hatten nur 4% davon eine Krankheitsdauer von unter 2 Jahren, sodass die Fallzahl nicht ausreicht, um eine Gruppen an inzident erkrankten Betroffenen auf komplexe Zusammenhänge hin zu untersuchen.

Im chinesischen (60) CSTAR (Chinese SLE Treatment and Research group) Register wurde über 5 Jahre erhoben, bei welchen Patient*innen sich permanente durch den SLE verursachte Organschäden entwickelt haben- diese waren überwiegend zu finden in der Niere (26%), dem muskuloskelettalen System (20%), dem neuropsychiatrischen System (12%) und der Lunge (11%). Hier wurden prävalente SLE-Patient*innen eingeschlossen. Selbst prospektive, bevölkerungsbezogene und langfristig angelegte Beobachtungsstudien wie die Nako-Gesundheitsstudie (61) können nicht helfen, mehr über Komorbiditäten zu Beginn der Erkrankung zu erfahren- denn durch die Seltenheit der Erkrankung ist zu erwarten, dass es im Rahmen der Nako nur zu einzelnen inzidenten SLE-Fällen kommen wird.

3.3. Alternative Erhebung von Komorbiditäten

Wie im vorherigen Kapitel beschrieben kann es bei der Erfassung von Komorbiditäten in Sekundärdaten und in Beobachtungsstudien zu Detektionsbias kommen. Um diese Problematik zu adressieren gibt es die Möglichkeit im Rahmen von Studien ausgewählte Komorbiditäten standardisiert zu erfassen. Goldstandard ist hier eine standardisierte Untersuchung geschulter Studienärzt*innen nach einem vorher definierten Protokoll. So werden z.B. im Rahmen der NAKO-

Gesundheitsstudie (62) standardisierte Messungen des Blutdrucks und der Lungenfunktion vorgenommen. So wird sichergestellt, dass z.B. eine Hypertonie für alle Studienteilnehmer*innen gleichermaßen bekannt ist. Nicht bei jeder epidemiologischen Studie ist es möglich, alle Teilnehmer*innen standardisiert auf Komorbiditäten zu untersuchen. Neben Arztberichteten Angaben gibt es die Möglichkeit, die Teilnehmer*innen selbst zu vorhandenen Komorbiditäten zu befragen. Hier ist nicht davon auszugehen, dass die direkte Frage nach der Komorbidität alleine eine ausreichend sensitive und spezifische Antwort bringt. Im Kapitel Parodontitis bei Patienten mit rheumatoider Arthritis wurde untersucht, wie gut ein patientenberichteter Fragebogen geeignet ist, um RA-Patient*innen mit Parodontitis zu identifizieren. Hier wurden Teilnehmer*innen der Früharthritis-Kohorte CAPEA (Course And Prognosis of Early Arthritis) zu ihrer Zahngesundheit befragt. Parallel wurden die behandelnden Zahnärzte gebeten zu berichten, ob eine Parodontitis besteht und (falls vorhanden) Röntgenbilder zur unabhängigen Begutachtung durch an der Studie beteiligte Zahnärzte zu senden. Ziel war es, aus den 12 Fragen zur Zahngesundheit diejenigen zu identifizieren, die die höchste Sensitivität und Spezifität aufwiesen um Parodontitis zu identifizieren. Es wurden sechs Fragen identifiziert, anhand derer eine Parodontitis mit einer Sensitivität von 85% und einer Spezifität von 57% identifiziert werden konnte. Insgesamt konnten mit den sechs ausgewählten Fragen Personen mit Parodontitis ähnlich gut wie beim Fragebogen von Coburn et al. (63) identifiziert werden. Überraschend war, dass mithilfe des Alters und der Zahnzahl diejenigen mit Parodontitis fast genauso gut identifiziert werden konnten (Sensitivität 92%, Spezifität 40%). Basierend auf diesen Ergebnissen ist es also umsetzbar, mit nur einer Frage (Zahnzahl) RA-Patient*innen mit moderater Trennschärfe in Parodontitis-Betroffene und Nicht-Betroffene einzuteilen. Insbesondere bei Studien, in denen die Teilnehmer*innen schon viele ausführliche Instrumente ausfüllen, stellt das eine gute Möglichkeit dar, die Anzahl an Fragen zu reduzieren. In der Kerndokumentation wurde die Frage nach der Zahnzahl in 2015 aufgenommen (64). Hier konnte eine relevante Assoziation von Entzündungsparametern mit der Zahnzahl (als Zeichen für Parodontitis) gezeigt werden: In der Gruppe der Zahnlosen war die BSG im Median 20 mm/h, in der Gruppe mit 1-

19 Zähnen 16 mm/h, in der mit 20-27 Zähnen 14 mm/h und in der mit 28 Zähnen 11 mm/h. Die Feststellung, ob eine Parodontitis vorliegt ist kein Selbstzweck, sondern geschieht einerseits mit dem Ziel, den Zusammenhang von RA und Parodontitis weiter zu untersuchen. Andererseits besteht die Möglichkeit, mit einer Behandlung der Parodontitis nicht nur die Zahngesundheit zu verbessern, sondern auch die Krankheitsaktivität der RA (insbesondere die Entzündungsparameter) zu senken. In einer randomisierten, kontrollierten Machbarkeitsstudie mit jeweils 30 RA-Betroffenen in der Behandlungs- und Kontrollgruppe zeigten de Pablo et al. (65), dass sich die Krankheitsaktivität nach Parodontitis-Behandlung verbessert. Es bleibt abzuwarten, ob in einer darauf aufbauenden größeren Studie der Unterschied in der RA-Krankheitsaktivität klinisch relevant unterschiedlich von der Kontrollgruppe sein wird.

Unabhängig davon kann die Empfehlung an alle von RA Betroffenen ausgesprochen werden, ein besonderes Augenmerk auf die Zahngesundheit zu legen.

Die größte Limitation der Methodik bei der Fragebogenentwicklung zur Erkennung von Parodontitis bei Patienten mit rheumatoider Arthritis war, dass keine zentrale Untersuchung durch Studienzahnärzt*innen erfolgte, sondern die behandelnden Zahnärzt*innen den Parodontitis-Status übermittelt haben. Es ist möglich, dass dadurch einige Parodontitis-Fälle nicht erkannt worden sind, was die Analyse verzerren könnte.

Insgesamt konnte gezeigt werden, dass eine passable Einschätzung des Parodontitis-Status anhand patientenberichteter Angaben bei RA-Patient*innen möglich ist.

4. Zusammenfassung

Für viele entzündlich-rheumatische Erkrankungen in Deutschland, insbesondere die axSpA ist die mittlere Diagnoseverzögerung immer noch inakzeptabel lang. Insbesondere Personen, bei denen Tests auf Rheuma-spezifische Antikörper wie z.B. ACPA negativ ausfallen oder bei denen genetische Marker wie HLA-B27 nicht vorhanden sind werden im Mittel zu spät diagnostiziert. Dies kann zu langfristig höherer Krankheitslast führen. Um eine frühere fachärztliche Diagnose und Behandlung zu ermöglichen, gibt es Früharthritis-Sprechstunden und Zuweiserprojekte. Für die Erkennung entzündlich-rheumatischen Erkrankung mit einer sehr hohen mittleren Diagnoseverzögerung, der axSpA wurden verschiedene Klassifikationskriterien getestet. Diese zielen auf die Erkennung entzündlichen Rückenschmerzes durch Hausärzt*innen und Patient*innen ab. Alle untersuchten Kriterien waren ähnlich gut geeignet, um Personen mit entzündlichem Rückenschmerz zu erkennen. Bisher konnten Kriterien, bei welchen Personen möglichst früh eine rheumatologische Abklärung erfolgen sollte durch moderne Verfahren wie z.B. maschinelles Lernen nur gering verbessert werden. Größere Aufmerksamkeit für die Erkrankungen bei hausärztlich niedergelassenen Ärzt*innen ist ein weiterer Ansatzpunkt, um die Diagnosesituation zu verbessern.

Für kürzlich diagnostizierte SLE-Patient*innen wurde gezeigt, dass die Erkrankung schon zu Beginn mit vielen Komorbiditäten einhergeht. Wegen des Detektionsbias in den verwendeten Daten lässt sich bisher nicht genau quantifizieren, wie viel stärker die Komorbiditätslast im Vergleich zu Kontrollen ohne Autoimmunerkrankung ist.

Eine wichtige Grundlage für die weitere Arbeit mit Krankenkassen-Abrechnungsdaten wurde gelegt: Es konnte gezeigt werden, wie gut ICD-10 Codes und verschiedene Algorithmen zur Identifikation von RA-Patient*innen mit patientenberichteten Diagnosen übereinstimmen. Basierend auf diesen Ergebnissen wird es in Zukunft möglich sein, je nach Fragestellung entweder relativ breit aber unspezifisch definierte RA-Kohorten oder eher spezifisch definierte RA-Kohorten, bei denen nicht alle Betroffenen enthalten sind in Abrechnungsdaten zu definieren.

Auch für die Erkennung Parodontitis-Betroffener RA-Patient*innen wurde Evidenz generiert. Der Zusammenhang von RA und Parodontitis kann in Zukunft auch in großen epidemiologischen Studien an RA-Betroffenen erforscht werden, auch wenn es nicht möglich ist, zahnärztliche Untersuchungen im Rahmen der Studie durchzuführen. Der patientenberichtete Fragebogen war ausreichend gut, um RA-Patient*innen mit Parodontitis zu identifizieren. In allen vorliegenden eigenen Arbeiten wird deutlich, dass die Verknüpfung verschiedener Datenquellen großes Potential darstellt, einige Fragestellungen in Zukunft besser bearbeiten zu können. Ideal wäre eine Verknüpfung von klinischen Daten und Abrechnungsdaten. So könnten die Vorteile der größeren klinischen Tiefe der ärztlich erhobenen Daten mit der größeren Vollständigkeit und Breite der Medikationsdaten in den Abrechnungsdaten kombiniert werden. Analysen für die rheumatologische Versorgungsforschung könnten so noch besser die Evidenzgrundlage für Entscheidungen in der Gesundheitspolitik liefern und damit letztendlich die Patientenversorgung in Deutschland verbessern.

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Erklärung

§ 4 Abs. 3 (k) der HabOMed der Charité

Hiermit erkläre ich, dass

- weder früher noch gleichzeitig ein Habilitationsverfahren durchgeführt oder angemeldet wurde,
- die vorgelegte Habilitationsschrift ohne fremde Hilfe verfasst, die beschriebenen Ergebnisse selbst gewonnen sowie die verwendeten Hilfsmittel, die Zusammenarbeit mit anderen Wissenschaftlern/Wissenschaftlerinnen und mit technischen Hilfskräften sowie die verwendete Literatur vollständig in der Habilitationsschrift angegeben wurden,
- mir die geltende Habilitationsordnung bekannt ist.

Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

……. ……..
Datum Unterschrift

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