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Assessing the Severity of Type 2 Diabetes Using Clinical Data Based Measures: a Systematic Review

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Conflicts of Interest

Novelty Statement

- Assessing diabetes severity is important and could help identify people in need for targeted therapies and benchmark healthcare services.

- This is the first systematic review of measures quantifying type 2 diabetes severity. More severe diabetes was associated with greater risks for hospitalisation and mortality. Assessing diabetes severity using real-world electronic health records is under-researched and underutilised in clinical care. None of the studies compared the utility or performance of the developed measures to the currently-used indices, mainly glycated haemoglobin (HbA_{1c}).

- Health records are suitable to assess diabetes severity. Contemporary, actionable, and validated disease-specific severity in large diabetes cohorts are needed.

Abstract

Aims

To identify and critically-appraise measures using clinical data to grade the severity of type 2 diabetes.

Methods

We searched MEDLINE, Embase and PubMed between inception-June 2018. Studies reporting on clinical data-based diabetes-specific severity measures in adults with type 2 diabetes were included. We excluded studies solely reporting other diabetes forms. After independent screening, the characteristics of the eligible measures including design and severity domains, the clinical utility of developed measures, and the relationship between severity levels and health-related outcomes were assessed.

Results

We identified 6,798 papers, from which 17 studies reporting 18 severity measures (32,314 participants, 17 countries) were included: diabetes severity index (8 studies, 44%); severity categories (7 studies, 39%); complications' count (2 studies,11%); or severity checklist (1 study, 6%). Nearly 89% of the measures included diabetes-related complications and/or glycaemic control indicators. Two of the severity measures were validated in a separate study population. More severe diabetes was associated with increased healthcare costs, poorer cognitive function, and significantly greater risks for hospitalisation and mortality. The identified measures differed greatly in terms of the included domains. One study reported on the use of a severity measure prospectively.

Conclusions

Health records are suitable to assess diabetes severity. However, the clinical uptake of existing measures is limited. The need to advance this research area is fundamental as higher levels of diabetes severity are associated with greater risks for adverse outcomes. Diabetes severity assessment could help identify people requiring targeted and intensive therapies and provide a major benchmark for efficient healthcare services.

Keywords: diabetes; severity; type 2 diabetes; electronic health records.

1. Introduction

Diabetes mellitus is a long-term metabolic condition associated with an increased risk of morbidity and premature mortality, with type 2 diabetes forming over 90% of all cases of diabetes [1]. Globally, the management of people with non-communicable long term conditions (such as diabetes and heart disease) forms one of the greatest challenges facing healthcare systems [2]. The prevalence of diabetes has risen rapidly [3, 4] contributing to an estimated 1.6 million deaths worldwide in 2016 [5]. The World Health Organization (WHO) estimates that diabetes was the seventh leading cause of death in 2016 [5]. The 'severity' of clinical conditions can be conceptualised as a progression of the underlying disease process, where increasing severity and the associated complications lead to increased treatment complexity and greater impact on clinical resources [6]. Assessing disease severity in diabetes is important because it: i) enables identification of people in greater need for more targeted and intensive therapies for risk stratification and to reduce adverse outcomes; ii) could optimise the allocation of healthcare resources towards those at greatest risk of harm; and iii) could provide a useful means of benchmarking clinical services. Currently, clinicians mainly use glycated haemoglobin (HbA$_{1c}$) levels as a proxy of diabetes severity and for management recommendations. However, using HbA$_{1c}$ levels is limited being a unidimensional measure, reliance is mainly on last recorded test, the quality of recorded data in primary care is questionable despite recent improvements. In addition, given the multi-organ involvement in diabetes, a more inclusive proxy for diabetes severity is recommended and needed.

The electronic recording of clinical records has developed substantially since its initiation in the 1980s [7] and becoming an important component underpinning clinical decision making and systematic care quality improvement [8]. Longitudinal electronic health records (EHRs) also enable the study of population health dynamics and form a powerful tool to improve the quality and value of health care services[9]. EHRs represent real-world data, and are expected to meet minimum standards for data quality [10, 11], and are inclusive of all patient groups encountered in routine clinical practice that are often excluded in clinical trials (pregnant women, children, the elderly, and people with multiple illnesses). Despite the widespread use of EHRs in healthcare systems across the world, they are not routinely used in quantifying the severity of

long-term conditions such as diabetes. Using such rich medical data to develop severity measures for diabetes could represent a practical aid for practitioners, supporting clinical management and service-planning.

Generic severity tools, such as the Charlson Comorbidity Index (CCI) [12] or the Duke Severity of Illness (DUSOI) checklist [13] are available but the applicability of such global measures of comorbid burden and their relevance specifically to people with diabetes, is unclear. Other tools have been developed that incorporate diabetes, such as the QRISK2 risk assessment tool (recommended to assess cardiovascular disease (CVD) risk in people with type 2 diabetes) [14] but this also provides limited information on diabetes severity. Furthermore, existing cardiovascular risk scores perform poorly in people with type 2 diabetes.[15] Considering the increasing disease prevalence, bespoke tools to assess diabetes severity need to be developed.

There has been no comprehensive review on the use of health records to develop a diabetes-specific severity indices and their predictive values. In this paper we present a critical review of studies that have quantified the severity of type 2 diabetes using medical data and EHRs. In our review we aimed to: i) describe the design, included domains and measured clinical outcomes of identified type 2 diabetes severity measures; ii) synthesize the association between type 2 diabetes severity levels and health-related outcomes; and iii) identify the likely best-performing severity measure(s) or with potentials of influencing clinical interventions based on the importance and clinical coherence of included severity domains, utility for primary care, and prospective association with clinical outcomes.

2. Methods

A protocol for this review is registered in the international prospective register of systematic reviews (PROSPERO registration number: CRD42018103147). Our review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and MOOSE guidelines [16, 17].

2.1.   Data Sources and Searches

We conducted our search of three main databases from inception to include all available studies. We searched MEDLINE (from 1964 to June Week 3, 2018) and Embase (from 1974 to June 20, 2018) using the OVID platform, and PubMed (from

inception to June 20, 2018). The searches consisted of four core blocks of terms in relation to 'diabetes', 'severity', 'grading' and 'stratification'. A combination of keywords and MeSH terms were used with appropriate Boolean operators. The detailed search strings are listed in Appendix S1. The search strategy was finalised by checking for coherence with prior scoping review results from Web of Science and PubMed.

2.2. Study Selection

Identified papers were considered eligible if they developed a system for grading the severity of type 2 diabetes using a model or algorithm utilising medical record data. Severity grading could be based on a simple count of severity domains, pre-defined categories of severity or on an assigned numerical score on a severity scale. No language or year restrictions were applied. Exclusion criteria included: i) non-research articles and examples of grey literature (such as case studies, conference proceedings, letters, commentaries or responses to articles); ii) studies not including an adult population or only including participants with other types of diabetes (such as type 1 diabetes or gestational diabetes); and iii) studies only applying previously developed severity indices, unless a substantial modification was conducted. If any methodological research was identified among the excluded applied research, it was agreed to only include the original work to the review.

In the first step, one reviewer (S.Z.) screened the references by titles and abstracts to assess eligibility and exclude irrelevant papers. The remaining potentially eligible papers were then assessed independently by titles and abstracts by two reviewers (E.K. and S.Z.) and any discrepancies were resolved by discussion. Cohen's kappa was used to measure the agreement between both assessments. Full-text review of eligible papers were screened by S.Z. A batch of the eligible papers was reviewed in full text by a second reviewer (E.K.). The two reviewers agreed on all decisions regarding inclusions and exclusions and therefore just one reviewer continued to screen full-text papers.

2.3. Data Extraction and Quality Assessment

One researcher (S.Z.) extracted relevant information from the final full-text papers in pre-designed MS Excel form, including: author(s), year of the study, country, and study population demographics (age, gender, duration of diabetes), study design, sample

size, variables included to assess severity, design of severity algorithm, the process of severity score assignment and score calculation, the outcome(s) associated with graded severity (if any), the measure validation (if conducted), and a summary of the main findings. Studies to be critically appraised using an appropriate quality assessment tool, based on the type of the identified studies.

2.4. Data synthesis and Analysis

The primary aim of this review was to identify and describe existing severity measures used to assess the severity of type 2 diabetes. The data were narratively synthesised and interpreted by:

1. Describing the characteristics and critically evaluating the design of measures used to define the severity of type 2 diabetes and identify the included severity domains (predictors that are relevant to the degree of progression of type 2 diabetes) and reported outcomes.
2. Synthesising the association between diabetes severity levels and health-related outcomes.
3. Identifying the best-performing measure(s) based on performance, the breadth of included severity domains and their relevance to primary care.

3. Results

Our search resulted in 6,798 studies, of which 3,555 duplicates were removed. The initial title (and abstract as needed) screening stage of the non-duplicate references resulted in the exclusion of 2,893 irrelevant articles. From the remaining 350 papers, which were screened independently by two authors (Cohen's Kappa rater agreement = 0.95), a further 332 papers were excluded and 18 articles were eligible for full-text review. Five of the 18 eligible papers were independently reviewed in full text by a second reviewer.

One study was excluded [18] after full-text review as a duplication of a previously-developed diabetes severity measure (already in our review) [19] by updating International Classification of Diseases (ICD) codes from ICD-9 to ICD-10. In agreement with our eligibility criteria, we retained the paper describing the original severity measure. The remaining 17 studies were included in the review. The search

and selection stages are illustrated in the PRISMA flowchart chart (Fig. 1). The PRISMA checklist is presented in Appendix S2 and the MOOSE checklist in Appendix S3.

No single quality assessment tool could be used to evaluate the included papers, due to their very different designs (e.g. risk prediction models, observational studies or other), since such tools include study-type-specific domains.

3.1.   Characteristics of the Included Studies

Overall, a total of 18 diabetes severity measures reported in 17 studies were evaluated. The included studies assessed diabetes severity using various approaches, primarily by using either severity categories or a numerical score. Table 1 presents a summary of the main participants' characteristics for each of the 17 studies included in the analysis. Of the identified studies, published between 1994 and 2018, the majority were based in the USA [19-26] while other studies originated from China [27], Denmark [28], Germany [29], Italy [30], the Netherlands [31], Spain [26], Japan [32], and Australia [33]. One study included participants from 16 countries (Australia, Austria, China, Czech Republic, Germany, Denmark, Spain, France, Hong Kong, Hungary, Italy, Japan, Korea, Poland, Russia, and the USA) [34]. No studies were identified from other countries well-known for their high availability of national administrative data, such as the UK. Ten studies were cross-sectional [19, 20, 23, 25, 28, 31-35]; six were retrospective [21, 22, 24, 26, 29, 30]; and only one reported a prospective design by assessing the relationship between longitudinal severity and clinical outcome [27]. The study populations consisted mainly of people with type 2 diabetes only (N=2,889 in 10 studies, 59%), but seven studies (41%) included participants with other forms of diabetes in addition to type 2 diabetes (mainly type 1 diabetes). These seven studies did not describe the distribution of participants by the type of diabetes, except in one study where participants with type 1 and type 2 diabetes formed 12% (N=492) and 88% (N=3,737), respectively [19]. The total population from all studies was 32,314 (including participants without diabetes for comparison), while the sample size of participants with diabetes was 15,283 (47%) and ranged in individual studies between 65 and 4,229 participants. In all, participants were aged between 30 and 90 years, of whom 0.0%-71% were women. Middle-aged and older people with type 2 diabetes [20], veterans, and first-time heart transplant recipients with diabetes were included in some of the eligible studies [22-25].

3.2. Characteristics of Diabetes Severity Measures

Details for the severity measures design, included domains and reported outcomes of diabetes severity outcomes across studies are presented in Table 2.

3.2.1. Severity Measures Design

Four different designs of diabetes severity measures were identified across the 18 included measures: i) developing a composite severity index or measure (8 measures, 44%); ii) using categories of disease severity (7 measures, 39%); iii) using a diabetes symptom checklist (1 measure, 6%); and iv) using a simple count of diabetic complications (2 measures, 11%).

i) Composite Severity Index or Measure

In these studies (8 studies across 11,138 participants), diabetes severity scores were either developed as a continuous scale or as a composite severity measure using pre-determined severity domains [19, 20, 22-26, 32]. Severity scales were based on assigning a score (a simple count or a weighted score) to each of the defined severity indicators, and from these individual scores, an overall score was calculated. These severity measures included clinical indicators including: body mass index (BMI), glycated haemoglobin (HbA$_{1c}$), diabetes duration, type and number of prescribed medications, renal function, blood pressure, and diabetes-related microvascular and macrovascular complications.

ii) Categories of Disease Severity

In studies using severity level categories (7 studies across 2,640 participants), participants were categorised as having between two to six levels of severity by pre-defined diabetes-related criteria [21, 27-30, 33, 35]. The categories were based on insulin use, diabetes therapy intensity, the presence of diabetes-related microvascular and macrovascular complications, glucose and HbA$_{1c}$ levels, diabetes duration, and history of hypoglycaemia.

iii) Simple Count of Diabetic Complications

In studies using a count of conditions (2 studies across 5,549 participants), diabetes severity was assessed based on a count of diabetes-related complications. In the first study, the severity assessment was based on a simple sum of the number of diabetic

microvascular and macrovascular complications in 4,229 participants with diabetes (type 1 diabetes and type 2 diabetes) from one US geographic region [19]. In the same study, the simple count was compared to a composite diabetes severity index (as described above) in predicting the risk of hospitalisation, healthcare utilisation and mortality. The second study included 1,320 participants with diabetic macular oedema enrolled from four studies in 16 countries [34]. The simple count was based on the sum of presence or absence of five conditions (pseudophakia, diabetic neuropathy, diabetic nephropathy, peripheral vascular disorder, and proteinuria). Each participant was assigned a score between 0 (for people without any of these conditions) and 5 (people with all five conditions).

iv)   Diabetes Symptoms Checklist

One study used a checklist developed to measure perceived symptom severity and assess change over time in 185 participants with type 2 diabetes [31]. The 34-item participant-derived clinical checklist categorised diabetes symptom severity into six clinical domains including: hyperglycaemic, hypoglycaemic, cardiovascular, psychological, neuropathic and ophthalmic. The sample size was however relatively small and the checklist was mainly based on participants' perception of diabetes severity.

3.2.2. Severity Domains

Diabetes-related complications were the most commonly used domains to assess diabetes severity, as reported in 11 (61%) of the severity measures [19, 21, 23, 25, 27, 28, 30-34]. Microvascular complications (diabetic neuropathy, nephropathy and retinopathy) and macrovascular events were included. Glycaemic control was the second most-commonly included domain, with levels of blood glucose and/or HbA_{1c} used in eight (44%) severity measures [21, 22, 26-29, 32, 35]. The complexity of anti-diabetic treatment domain was also used in four (22%) severity measures and was assessed as insulin use and/or the number of prescribed anti-diabetic therapies (monotherapy versus drug combinations) [20, 29, 30]. Other domains used to assess diabetes severity were diabetes duration [26, 35]; blood pressure levels [22, 28]; the presence of renal disease (levels of albuminuria [28] and/or serum creatinine) [19, 22, 25]; a composite score of: quality of life indicators and counts of comorbidities and prescribed medications [20]; demographic variables (age, gender, ethnicity, marital

status) [22]; BMI [22]; low density lipoprotein (LDL) levels [22]; a composite history of: cerebrovascular and/or cardiovascular disease, severe obesity, and renal failure before heart transplantation [24].

3.2.3. Measured Outcomes

The measured outcomes varied form general measures of use of healthcare resources and measures of health-related outcomes. In all, the clinical outcomes most-frequently related to diabetes severity levels were the risk for hospitalisation (one study),[19] healthcare utilisation and/or costs (three studies) [21, 22, 33], and mortality (three studies) [19, 24, 33] . Less-frequently, other outcomes assessed in relation to diabetes severity in individual studies included haematological changes[32], physical or cognitive function [20, 23, 35] , changes in diabetes therapy after bariatric surgery [29]; long-term diabetes remission and selection of metabolic surgery [26]; obesity-associated protein expression [27]; and participant satisfaction [25]. Four studies have validated the developed severity measures using a separate dataset or by mapping them to clinical outcomes [19, 22, 26, 33]. One study used positive predictive value (PPV) to assess the developed type 2 diabetes severity measure (Table 2) [30].

3.3. Synthesising the Association between Severity Levels and Health-Related Outcomes

The studies that assessed diabetes severity and hospitalisation found that higher severity was associated with significantly greater risk for hospitalisation [19]. Assessing the relationship between severity of diabetes and healthcare costs and adverse events revealed that worsening diabetes was associated with higher mean monthly in-patient costs, pharmaceutical and medical costs [21, 22, 33], and significantly increased risk for mortality [19, 33]. Severity of diabetes was also related to lower patient satisfaction with diabetes care received, cognitive dysfunction and significantly higher risks for adverse outcomes - mainly mortality [19-21, 25, 33]. Diabetes severity levels were also associated with immunological and haematological changes [32]. Table 2 details the association between measured severity and outcomes reported in the included studies. The first of the two studies that validated the severity measures in a separate population (Spain) reported similar findings to those found from the training dataset (USA) [26]. The second study reported differences between both datasets in the association between diabetes severity and one of two examined outcomes [22].

3.4. Clinical Performance of Diabetes Severity Measures

Among the included studies that developed a severity index, the measure reported by Young et al. (2008) was potentially the most comprehensive, since it included relevant severity domains routinely-recorded in primary care: diabetes-related complications, insulin use, and laboratory data and also compared two measures for diabetes severity. The study also included a relatively large population of 4,229 participants (the largest sample size among all identified studies) from clinics with a large ethnic diversity. The developed diabetes complication severity index (DCSI) was validated using clinical adverse outcomes and the results indicated that each increasing level of the DCSI was associated with a significantly greater risk for hospitalisation (HR: 1.29, 95% CI: 1.25; 1.32) and mortality (HR: 1.34, 95% CI: 1.28; 1.41) [19]. Additionally, when compared to a simple count of diabetes complications, determined also in the same study, both measures predicted 2-year mortality well, but the DCSI performed significantly better (P<0.0001) as indicated by comparing the area under the curve (AUC) of the receiver operating characteristics (ROC) curves of both severity measures (0.76 and 0.74). However, the measure did not include non-insulin anti-diabetic therapies, diabetes duration, and other comorbidities such as hypoglycemia.

It is noticeable that none of the studies compared the utility or performance of the developed severity measures to the currently-used main clinical proxy for diabetes severity $HbA_{1c.}$

In addition, only few examples of diabetes severity assessments potentially influencing clinical care were reported. The first came from a study reporting that diabetes severity was significantly associated with cognitive measures and self-care [20]. On that study, Gatlin et al. concluded by recommending that it is important for clinicians to consider cognitive measures (namely working memory and executive function) when assessing self-care in people with diabetes given that the three clinical components (diabetes severity, cognitive measures and self-care) appeared to be highly inter-related. In the second example, Wang et al. found that fat mass and obesity-associated (FTO) protein levels (that positively correlate to waist circumference, BMI and blood glucose indices)) increased with increasing type 2 diabetes severity, but significantly declined following a 12-week treatment in comparison to before treatment [27].

4. Discussion

4.1.　　Summary of Main Findings

Main findings: This systematic review aimed to provide an overview of existing measures assessing the severity of type 2 diabetes using clinical data. Our review has shown that there has been little development with practical applications of diabetes-specific severity measures. We found that: i) the most commonly used clinical variables for grading type 2 diabetes severity were diabetes-related complications and glycaemic control measures; ii) only a few studies considered the type or patterns of prescribed (diabetes and non-diabetes) therapies as a proxy for higher severity or assessed changes in diabetes severity over time or how therapeutic interventions could influence these changes; iii) measured diabetes severity was assessed in association with various health-related outcomes, mainly risk for hospitalisation, healthcare costs, and death; iv) none of the studies looked at the utility of the severity measures in adding prognostic information to the currently-used clinical measures, such as HbA_{1c}, and few explicitly presented new actionable severity tools to help clinicians target intervention more effectively.

Studies linking severity with outcome and studies with potential clinical applications: In relation to measured outcomes, the studies unsurprisingly showed that higher diabetes severity was associated with significantly higher risks for hospitalisation and mortality, increased healthcare costs, poorer cognitive function, and significantly lower participant satisfaction. However, only few examples of diabetes severity measures with potential influence on clinical care were reported.

Strengths and limitations of included studies: The earliest study identified in our review was in 1994 while others dated between 2002 and 2018, which indicates an increasing interest in this area. The studies were based in 17 countries and collectively included a wide range of clinical information relevant to diabetes severity, which could inform future measures of diabetes severity. Most of the reported measures and scoring approaches considered diabetes-specific severity indicators such as diabetes-related complications and glycemic level (mainly HbA_{1c}). However, while acknowledging the informative nature of the included studies, some severity measures missed other clinical data such as diabetes duration, hypoglycemia and CVD, while others included domains less applicable to the majority of people with type 2 diabetes

such as severe obesity or cerebrovascular accident (CVA). Moreover, some of these measures were applied in small cohorts, or in selective cohorts that are rarely encountered in non-specialist clinical practice settings. None of the identified measures were used prospectively or shown the impact on clinically relevant health-related outcomes, apart from the aforementioned examples by Gatlin and Wang [20, 27]. We have emphasised on the only longitudinal study identified in our data synthesis, as reporting on the prospective use of diabetes severity measures is an important dimension which can impact on clinical outcomes. A major limitation of existing severity measures is that they are based on cross-sectional data when clinical decisions are taken on implicitly longitudinal, multi-dimensional disease trajectories rather than a single measure. Only one of the included studies actively sought the patients' perspectives into the development of disease severity measures. Active involvement of patients in future studies is crucial for developing meaningful disease severity measures. To sum up, all studies showed early stages of development of tools, primarily severity categories and numerical scores. Thus very few studies have explored practical implications.

We focused on the clinical rather than methodological characteristics of the included diabetes studies and severity measures. Given the widely different designs of the included studies, no consistent quality assessment tool could be applied successfully to evaluate the included papers as the tools' specific criteria are not applicable to the included heterogeneous studies.

Challenges and clinical opportunities of developing diabetes severity scores:
Our review of the literature has shown that there has been little development and few practical applications of diabetes-specific severity indices. There is therefore considerable scope to work towards advances in refining these indices as reliable and practical tools for: i) identifying people by stage of disease to target and expedite interventions; ii) monitoring longitudinal trajectories of disease severity or serving as an outcome variable (resembling the Patient Reported Outcome Measures (PROMs)), for instance assessing the effect of interventions on the changes in severity; iii) predicting long term prognosis and underpinning clinical decision support systems for different management strategies; iv) inform planning resources for diabetes care in national health systems; and v) acting as an actionable tool that can influence therapeutic strategies and impact on hard clinical outcomes.

Opportunities for future research into diabetes severity scores: The clinical manifestations of more severe type 2 diabetes are a consequence of diverse and complex pathophysiological processes affecting different organ systems over time, making it difficult for a single severity measure to capture this complexity adequately. However, further alterations to existing measures would be more appropriate to develop severity measures for applications in different areas such as clinical practice and research. Many previous studies have relatively failed to capture this complexity and disease severity because they have omitted important clinical variables. Despite the presence of some diabetes-specific severity indices, we could not identify universal agreement around: i) the optimal data needed to create a reliable severity measure; ii) which severity measures perform better than others especially in predicting health outcomes; iii) or whether the developed models are actionable and would enable self-care and healthcare professionals to manage diabetes more effectively and improve clinical outcomes. Future research could also benefit from patients' and carers' perspectives of disease progression in diabetes assessing how patient opinion could influence decision making in diabetes care. Future studies developing diabetes severity measures should include domains that are routinely-collected in clinical practice and well-recorded in EHRs, in order to allow the implementation of these tools in practice.

4.2. Limitations and Strengths of This Review

Our review is limited, firstly, by excluding studies reporting only on other forms of diabetes. Although measuring the severity of other forms, mainly type 1 diabetes, could be relevant, our focus was on adults with type 2 diabetes in adult population because this represents ~90% of all diabetes. Secondly, some of the studies were based on people with diabetes managed in specialist facilities and not in routine clinical settings, such as veterans and individuals undergoing heart transplantation. Therefore, the findings in these selective populations are only likely to be applicable in these specific groups and may not generalise well to the wider type 2 diabetes population seen mostly in primary care. Thirdly, given the scope of this review and the heterogeneous design of included studies, we were not able to critically appraise the studies using available and recognised quality assessment tools. Our review has several strengths: firstly, to our knowledge this is the first systematic review identifying

measures quantifying the severity of type 2 diabetes using medical data, mostly collected in clinical settings. Secondly, we used a broad search strategy; inclusion criteria had no restriction on year or language. Thirdly, two independent reviewers performed the second screening stage. Finally, the review was conducted and recorded in accordance to the PRISMA guidelines [16].

4.3.   Implications

<u>Clinical need and research implications:</u> These findings indicate the potentials of disease-specific severity measures derived by clinical data with applications in clinical practice in future research. Such measures will allow researchers to better map and quantify disease trajectories, in relation to health-related and social outcomes, improving clinical trials and observational studies, and eventually allow clinicians to use these measures in practice to provide more individualised healthcare. Also, severity scores might help improve risk stratification enabling safer delegation of care within the clinical team, and provide a more clinically relevant tool than the currently used proxy, HbA_{1c}. Although current guidelines for management of type 2 diabetes are satisfactory in terms of treatment recommendations, but with an ageing population in many countries concerns have been raised regarding the lack of comprehensive recommendations that would address the rapidly increasing prevalence of multimorbidity (the main component of the disease severity scores). In addition, current guidelines, mainly comment on the severity of individual components of diabetes (severe hypoglycaemia, severe neuropathy, etc) but not severe diabetes. Therefore, a composite score that encompasses all relevant severity domains in people with diabetes may be needed. Importantly, the recent consensus report by the ADA and the EASD included a recommendation for providing patient-centred care that takes multimorbidity into account [36]. Future clinical guidelines for management of type 2 diabetes need to provide more comprehensive recommendations that would help healthcare professionals to address the rapidly increasing prevalence of multimorbidity, a main indicator of increasing disease severity, in people with type 2 diabetes. Further research is needed as the potential for these developments is particularly high in countries where primary care EHRs or national disease registries contain comprehensive, clinician-coded data, often supported by financial incentives [37, 38]. A more inclusive severity index validated using important clinical outcomes in

a large diabetes population cohort, will be welcome. Such a measure would serve as an important proxy for health status and in decision making in diabetes care.

Generalisability: Our findings may have greatest generalizability in countries that have access to routinely-collected administrative data, as evidenced by the numerous countries in which these studies were conducted and the heterogeneity of the study populations. Unsurprisingly, the more recently developed severity measures appear to be more promising and better-founded - supported by the rapidly growing availability of clinical data and well-characterised diabetes cohorts. This and the quick evolution of rich EHRs offer an unprecedented opportunity to use these clinical data to develop comprehensive measures assessing diabetes severity and optimal impact in clinical care.

In conclusion, this systematic review highlights that the assessment of type 2 diabetes severity using routinely-collected real-world clinical and administrative data is under-researched and underutilised in clinical care. Ideally, more inclusive type 2 diabetes severity measures would be developed using a large collection of high-quality longitudinal EHR data from heterogeneous populations or settings. In addition, study of the performance of such measures in comparing groups and predicting outcomes would be fed back, at scale, to inform the improvement of the measures. The existence, development and evolution of high quality EHRs would further improve quantification of diabetes severity, which would help identify people with diabetes at need for targeted interventions, support clinical decision making, and also expected to lead to major clinical and healthcare benefits in the future.

Funding

Conflicts of Interest

List of Abbreviations

aHR: adjusted hazard ratio**; AUC**: area under the curve; **BMI:** body mass index; **CCI**: Charlson Comorbidity Index; **CI**: confidence interval; **CVA:** cerebrovascular accident; **CVD**: cardiovascular disease; **DCSI**: diabetes complications severity index; **DRC:** diabetes-related complications; **DUSOI:** the Duke Severity of Illness; **EHR**: electronic health record; **FTO**: fat mass and obesity-associated gene; **HbA$_{1c}$:** glycated haemoglobin; **HSC**: health status composite; **ICD**: International Classification of Diseases; **IMS:** individualised metabolic surgery**; LDL:** low density lipoprotein; **PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **PVD:** peripheral vascular disease; **ROC**: receiver operating characteristic; **WHO:** World Health Organization.

Some of the data are presented at The Society for Academic Primary Care (SAPC) North Conference, November 2018, Kendal, UK

Supporting Information
Appendix S1 Detailed search strategy in three databases
Appendix S2 PRISMA Checklist
Appendix S3 MOOSE Guidelines Checklist

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Table 1 Descriptive data of the design and study population characteristics of the included studies. * Reporting on the size of diabetes population if the study also included participants without diabetes. †Age presented as mean (±SD) unless otherwise stated.

Study number and Author-Year	Study design	Study population size*	Age, years (±SD)†	Gender (women) N (%)	Country
1. Aminian et al. 2017 [26]	Retrospective study	N=900 (TD: N=659; VD: N=241)	TD: 51 (±10) VD: 52 (±9.0)	TD: 451 (68) VD: 158 (66)	USA/Spain
2. Brazier et al. 2017 [34]	Cross-sectional study	N=1,320	61.7 (±9.7)	580 (43.9)	Australia, Austria, China, Czech Republic, Germany, Denmark, Spain, France, Hong Kong, Hungary, Italy, Japan, Korea, Poland, Russia, and USA
3. Gatlin et al. 2015 [20]	Cross-sectional study	N=67	62.9 (±10.9)	37 (55.2)	USA
4. Gibson et al. 2012 [33]	Cross-sectional study	N=379	48 (±12.5)	220 (58)	Australia
5. Gini et al. 2016 [30]	Retrospective study	N=300	NA	NA	Italy
6 Grootenhuis et al. 1994 [31]	Prospective study (cross-sectional data on the relationships between diabetes severity and health outcomes were only provided)	N=185	65 (±11)	88 (48)	Netherlands
7. Joish et al. 2005 [22]	Retrospective study	N=734	65.9 (±10.3)	24 (3)	USA
8. Kerr et al. 2003 [25]	Cross-sectional study	N=1,314	67 (±11)	26 (2)	USA
9. Linzer et al. 2005 [23]	Prospective study (cross-sectional data on the diabetes severity tool were only provided)	N=65	64 (NA)	None (0)	USA
10. Munch et al. 2016 [28]	Cross-sectional study	N=664	64.4 (range 19-93)	280 (42.2)	Denmark

Study number and Author-Year	Study design	Study population size*	Age, years (±SD)†	Gender (women) N (%)	Country
11. Okano et al. 2008 [32]	Cross-sectional study	N=142	Range 30-90 (NA)	54 (31.7)	Japan
12. Rosenzweig et al. 2002 [21]	Retrospective study	N=508	41.8 (±10)	231 (45.5)	USA
13. Runkel et al. 2015 [29]	Retrospective study	N=77	48.5 (±8.5)	55 (71.4)	Germany
14. Russo et al. 2006 [24]	Retrospective study	N=3,687	55.8 (±7.9)	745 (20.2)	USA
15. Schneider et al. 2017 [35]	Cross-sectional study	N=602	75 (NA)	381 (63.3)	USA
16. Young et al. 2008 [19]	Prospective study (cross-sectional data on the diabetes severity tool were only provided)	N=4,229	63.21 (±13.3)	2,040 (48.2)	USA
17. Wang et al. 2018 [27]	Cross-sectional study (12 weeks prospective design for the severe diabetes group)	N= 110	• Mild severity group: 50.3 (±4.2) • Severe group: 52.0 (±3.3)	• Mild severity group: 30 (52) • Severe group: 25 (48)	China

Abbreviations: **NA**: not available; **SD:** standard deviation; **TD**: training dataset; **VD**: validation dataset.

Table 2 Summary of the severity measures design, included domains and measured health-related outcomes.

Study number and Author-Year	Characteristics				Association with health-related outcomes	Severity measure validated (Yes/No)
	Severity Measure Design	Severity Domains	Severity sub-domains (if any)	Outcomes		
1. Aminian et al. 2017 [26]	Individualised metabolic surgery (IMS) score	Preoperative: • Insulin use • The number of diabetes medications • Diabetes duration • HbA$_{1c}$ level	-	Type 2 diabetes remission rate and selection between two bariatric surgeries	Remission rates decreased with increasing diabetes severity. Both surgeries showed significant improvements in remission rate irrespective of the severity of type 2 diabetes.	Yes
2. Brazier et al. 2017 [34]	Count of diabetic complications (score 0 -5)	Diabetes-related complications	• Pseudophakia • Neuropathy • Nephropathy • PVD • Proteinuria	The relationship between visual acuity and utility (HRQoL)	The relationship between visual acuity and utilities attenuates with increasing diabetes severity.	No
3. Gatlin et al. 2015 [20]	Modified diabetes care profile measure	• Health status composite (HSC) • The number of medications and comorbidities	HSC derived from quality of life domains related to: • Physical function • Pain • General health	Association between cognitive function, self-care and type 2 diabetes severity	Higher severity was associated with cognitive dysfunction, where the working memory measure was significantly correlated with the diabetes severity variables (HSC (r= 0.542, P<0.01); the number of prescribed medications (r= -0.344, P < 0.01); and the number of comorbid conditions (r= -0.476, P < 0.01)).	No
4. Gibson et al. 2012 [33]	Four stages of diabetes severity	• Microvascular complications • Macrovascular complications	• Retinopathy • Neuropathy • Nephropathy • Cerebrovascular disease • Cardiovascular disease • PVD	• In-patient hospital costs • Mortality	Worsening diabetes severity was associated with increased hospital costs and mortality.	Yes

Study number and Author-Year	Characteristics				Association with health-related outcomes	Severity measure validated (Yes/No)
	Severity Measure Design	Severity Domains	Severity sub-domains (if any)	Outcomes		
5. Gini et al. 2016 [30]	4-level severity categories	• Insulin therapy • Microvascular complications • Macrovascular complications	• Retinopathy • Diabetic foot ulcer • Lower limb amputation • Nephropathy • Dialysis • Cardiovascular disease	• Positive predictive value (PPV) for automated algorithm absence/presence of type 2 diabetes • Agreement between automated algorithm and GP on severity level	High PPV (100%) for type 2 diabetes detection. High agreement score (Cohen's kappa=0.7) between automated algorithm and GP assessment.	Yes
6. Grootenhuis et al. 1994 [31]	A checklist for diabetes severity	Six dimensions: • Hyperglycaemic • Hypoglycaemic • Cardiovascular • Psychological • Neuropathic • Ophthalmic	Cardiovascular: • Shortness of breath • Chest pain Psychological: • Sense of fatigue • Moodiness	• Measure differences in severity between participants • Assess severity over time • Compare mean severity scores in participants with different comorbidity status and treatment mode	The patterns of comorbidities and prescribed treatments were reportedly associated with significant differences in the estimated severity scores. The checklist was found to be a useful diabetes-specific assessment tool for clinical studies with ability to detect change over time.	Yes
7. Joish et al. 2005 [22]	A diabetes severity index (DSI)	10 variables in: • Demographic measures • Glycaemic • Renal • Cardiovascular health status	• Age, gender, ethnicity, marital status, BMI • HbA$_{1c}$ • Creatinine clearance • Systolic and diastolic blood pressure, LDL level.	Healthcare resource use and costs	Higher diabetes severity was associated with higher expenses and healthcare utilisation.	Yes
8. Kerr et al. 2003 [25]	Diabetes related components of the Total Illness	• Microvascular complications	• Diabetic eye disease	Participants satisfaction with provided care and communication	Individuals with higher diabetes severity reported lower satisfaction with subject-provider communication and overall diabetes care	No

Study number and Author-Year	Characteristics				Association with health-related outcomes	Severity measure validated (Yes/No)
	Severity Measure Design	Severity Domains	Severity sub-domains (if any)	Outcomes		
	Burden Index (DM TIBI)	• Macrovascular complications • Hypertension • Renal insufficiency • Obesity	• Diabetic foot complication • Coronary artery disease • Congestive heart failure			
9. Linzer et al. 2005 [23]	Diabetes severity measure (DMSEV)	• Microvascular complications • Macrovascular complications	• Eye, foot or neuropathic symptoms • TIA • Stroke • Myocardial infarction • Chest pain frequency • Claudication	Validation of participant-based assessment measure of type 2 diabetes severity by correlating to DMSEV measure	High correlation between the DMSEV and all outcomes in the participant-based assessment (particularly was highly associated with physical function) concluding that the participant-based assessment questionnaire and DMSEV are valid measures of diabetes severity.	Yes
10. Munch et al. 2016 [28]	Three levels of severity	• HbA$_{1c}$ • Blood pressure • Metabolic complications • Microvascular complications • Macrovascular complications	• Insulin resistance • Glucose levels • Retinopathy • Diabetic foot disease • Nephropathy • Major cardiovascular event • PVD	• Measure compliance of endocrinologists to risk stratification guidance. • Investigate the level of concordance between stratification performed by the endocrinologists and objective assessments	High compliance of endocrinologists to the Danish guidelines, which recommends the stratification of participants into three risk stratification levels according to risk and complexity of anti-diabetic treatment, was reported	No
11. Okano et al. 2008 [32]	Severity index 13-point scale (scores 0-12)	• HbA$_{1c}$ • Diabetes-related complications	• Hypertension • Hyperlipidaemia • Atherosclerosis • Retinopathy • Neuropathy	Haematological and immunological changes (counts of white blood cells, platelets and lymphocytes)	Different levels of diabetes severity were associated with differences in immunological and haematological levels. The severity index was positively associated with neutrophil counts and	No

Study number and Author-Year	Characteristics				Association with health-related outcomes	Severity measure validated (Yes/No)
	Severity Measure Design	Severity Domains	Severity sub-domains (if any)	Outcomes		
			• Nephropathy		negatively associated with platelet and CD19+ lymphocyte counts.	
12. Rosenzweig et al. 2002 [21]	4-level severity categories	• Diabetes-related complications • Glycaemic control • Cardiovascular disease	• Eye disease • Neuropathy • Renal disease • Congestive heart failure • PVD	• Total medical and pharmaceutical costs • Management of comorbidities	Participants with very-high and high risk severity levels were found to have markedly increased costs compared to participants in the lower risk groups. Nearly 26% of the total diabetes costs were attributed to long term complications	No
13. Runkel et al. 2015 [29]	6-level severity categories	• Anti-diabetic treatment complexity • Glucose levels	Anti-diabetic treatment: •No therapy •Diet •Oral therapy •Insulin •Oral and insulin •Poor control despite therapy	Downgrading of type 2 diabetes (reduction in diabetes severity)	Preoperative diabetes severity independently predicted postoperative reduction in diabetes severity. Participants with lower pre-existing diabetes severity and shorter duration of diabetes benefited the most from surgery.	No
14. Russo et al. 2006 [24]	Diabetes-related complications (DRC) aggregated measure	History of: • Cerebrovascular accident (CVA) • PVD • Severe obesity • Pre-heart transplantation renal failure	-	Survival time post heart transplantation	Diabetes severity was related to the risk of adverse events post-transplantation. Survival after heart transplant was inversely related to diabetes severity (DRC). Median post-transplant survival was 9.3 years in participants with no DRC; 6.7 years in participants with one DRC; and 3.6 years in participants with ≥2 DRCs.	No
15. Schneider et al. 2017 [35]	2-level severity categories	• Diabetes duration • HbA$_{1c}$ level	-	Subclinical brain pathology	Participants with more-severe diabetes (defined by higher HbA$_{1c}$ or longer diabetes duration) had greater burden of brain vascular pathology than participants with less-severe diabetes.	No

Study number and Author-Year	Characteristics				Association with health-related outcomes	Severity measure validated (Yes/No)
	Severity Measure Design	**Severity Domains**	**Severity sub-domains (if any)**	**Outcomes**		
16. Young et al. 2008 [19]	• Count of diabetic complications • Severity index 14-point scale (scores 0-13)	• Diabetes-related complications	• Retinopathy • Neuropathy • Nephropathy • Cerebrovascular disease • Cardiovascular disease • PVD • Ketoacidosis • Hyperosmolar and other coma	• Mortality • Risk of hospitalisation	The count of diabetes-related complications was associated with higher risk for mortality. Compared to participants with no complication (referent), those with one complication had no increased risk; those with three complications had a 3-fold higher risk of death (adjusted hazard ratio (aHR): 2.7, 95% CI: 1.8; 4.0), and with ≥5 complications had a 7-fold higher risk (aHR: 7.2, 95% CI: 4.4; 11.7). Higher diabetes severity score was associated with a higher risk for hospitalisation and death. A one-level higher diabetes severity score was associated with a 1.3-fold higher risk of death (95% CI: 1.25; 1.32).	Yes
17. Wang et al. 2018 [27]	2-level severity categories	• HbA$_1$ • Diabetes-related complications	• Retinopathy • Nephropathy	Correlation with fat mass and obesity-associated (FTO) gene expression	Participants with severe diabetes showed significantly higher FTO expression levels in comparison to participants with mild diabetes. Levels of FTO protein were found to be significantly associated with waist circumference, BMI and blood glucose measures.	No

Abbreviations**: aHR:** adjusted hazard ratio; BMI: body mass index; **CI**: confidence interval; **DMSEV**: Diabetes severity measure; **DRC**: diabetes-related complications**; FTO**: fat mass and obesity-associated; **GP:** general practitioner**; HbA$_{1c}$:** glyated haemoglobin**; HRQoL**: health-related quality of life; LDL: low density lipoprotein; **PPV**: Positive predictive value; **PVD**: peripheral vascular disease; TIA: transient ischemic attack.

Figure legend

Figure 1 PRISMA flow diagram for search and selection strategies for the included studies