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Pre-existing diabetic retinopathy as a prognostic factor for COVID-19 outcomes amongst people with diabetes: A systematic review

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Diabetes Research and Clinical Practice

PRE-EXISTING DIABETIC RETINOPATHY AS A PROGNOSTIC FACTOR FOR COVID-19 OUTCOMES AMONGST PEOPLE WITH DIABETES: A SYSTEMATIC REVIEW

--Manuscript Draft--

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Abstract:	<p>Aims Certain patients with Diabetes Mellitus (DM) have high risk for complications from COVID-19. We aimed to test the hypothesis that pre-existing diabetic retinopathy (DR), a microvascular disease, is a prognostic indicator for poor COVID-19 outcome in this heterogeneous population.</p> <p>Methods Seven databases (including MEDLINE) and grey literature were searched, identifying eligible studies using predetermined selection criteria. The Quality in Prognosis Studies (QUIPS) tool was used for quality assessment, followed by narrative synthesis of included studies.</p> <p>Results Eight cohort studies were identified. Three showed significant positive associations between DR and poor COVID-19 outcomes. The highest quality study, McGurnaghan, found increased risk of the combined outcome fatal or critical care unit (CCU)-treated COVID-19 with referable-grade DR (OR 1.672, 95% CI 1.38–2.03). Indirectly, four studies reported positive associations with microvascular disease and poorer prognosis. Variability between studies limited comparability.</p> <p>Conclusions The current literature suggests an independent association between DR and poorer COVID-19 prognosis in patients with DM after controlling for key variables such as age. The use of standardised methodology in future studies would establish the predictive value of DR with greater confidence. Researchers should consider comparing the predictive value of DR and its severity, to other microvascular complications of DM.</p>
Opposed Reviewers:	
Response to Reviewers:	

Isabel Boden
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EH16 4SB

3 January 2022

Dear Professor Cariello,

I am pleased to submit an original research article for consideration by Diabetes Research and Clinical Practice: *"Pre-existing Diabetic Retinopathy as a prognostic factor for COVID-19 outcomes amongst people with diabetes: a Systematic Review"*.

Evidence has emerged throughout the COVID-19 pandemic to indicate that people with diabetes are at higher risk of poor outcomes and it has been hypothesised that people with pre-existing microvascular disease, such as diabetic retinopathy, are at particularly elevated risk. The challenge of conducting clinical and scientific studies during a global pandemic in addition to the heterogeneous nature of diabetes itself means that a systematic review is urgently required. Here, we provide an overview of the evidence base around whether diabetic retinopathy (a relatively accessible indicator of microvascular disease) has the potential to be a useful risk stratification tool.

We searched extensively for relevant literature and found eight cohort studies. The highest quality study found increased risk of the combined outcome fatal or critical care unit (CCU)-treated COVID-19 with referable-grade diabetic retinopathy (OR 1.672, 95% CI 1.38–2.03) and two others reported poorer COVID-19 prognosis associated with diabetic retinopathy. Four studies reported an association between poor COVID-19 prognosis and microvascular disease, including diabetic retinopathy. The two smallest studies found no association.

While these results are suggestive of a positive independent association between diabetic retinopathy/microvascular disease and poorer COVID-19 outcomes, variability between study outcomes and definitions was a significant factor limiting comparison. We therefore stress the importance of standardised outcomes in future research to comprehensively investigate the predictive power of retinopathy as an objective, quantifiable biomarker.

As one of the key journals publishing scientific and clinical research related to diabetes, we believe that this review is a perfect fit for your readership; it is centred upon improving patient care for people with diabetes through risk stratification during the ongoing COVID-19 pandemic.

We have no conflicts of interest to disclose and confirm that this work is original and has not been published elsewhere, nor is it currently under consideration for publication elsewhere. Please address all correspondence concerning this manuscript to me at, I.Boden@sms.ed.ac.uk.

Thank you for your consideration of this manuscript.

Yours sincerely,

Isabel Boden

Re-submission reviewers' comments and authors' detailed responses

Reviewer #1: This paper is a well written article which presents an interesting topic studying the impact of diabetic retinopathy on covid-19 outcome.

While it is interesting that this study provides evidence on the impact of DR on worse covid outcomes, it **does not add further information of the mechanism nor the impact of this finding on clinical care.**

Thank you for your insightful comments and suggestions for improvement to the manuscript.

- With regards to suggesting a mechanism for why diabetic retinopathy is associated with worse covid-19 outcomes, this was not the focus for this review so we have not systematically evaluated current theories on this, but agree that this would be a useful point on which to expand. We already mention in the introduction that COVID-19 itself manifests as a widespread microvascular disease, noting that those with pre-existing microvascular disease are thus more at risk and suggest that further research could helpfully address this point. To further emphasise and elucidate this important point, we have added details from selected sources about proposed mechanisms to the discussion.
- Regarding impact on clinical care, we have further reinforced the clinical significance of this review in the manuscript. Please see the changes in section 4.2.

Diabetic retinopathy has been reported to be associated with increased risk of other microvascular and macrovascular complications of DM. I would suggest the author not only discuss about its association with diabetic nephropathy but also diabetic cardiomyopathy or heart failure which may as well also contributing the increased risk of worse covid outcome. The presence of hypertension and Dyslipidemia would also contribute to DR and also worse covid outcome. Other factors such as obesity, HbA1c levels, duration of DM could also contribute.

Thank you for this interesting point regarding the prognostic potential of other microvascular diseases. As nephropathy was also mentioned in the review, it would be fair to include the prognostic potential of other prognostic factors, such as macrovascular diseases, hypertension and dyslipidaemia. Consequently, we have added a short section in section 4 (Discussion) to compare these associations to that of diabetic retinopathy and/or microvascular disease. Overall, findings were interesting and supportive of microvascular disease being more strongly associated with poorer COVID-19 prognosis than other accessible measurements. However, regarding heart disease the difference in association remains inconclusive among the papers included in the review.

Reviewer #2: An interesting and novel contribution with fair data presentation and discussion.

Thank you for your supportive and informative comments regarding the manuscript.

PRE-EXISTING DIABETIC RETINOPATHY AS A PROGNOSTIC FACTOR FOR COVID-19 OUTCOMES AMONGST PEOPLE WITH DIABETES: A SYSTEMATIC REVIEW

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Highlights

- Severe diabetic retinopathy (DR) was independently associated with poorer outcomes of COVID-19, including need for critical care or death.
- Microvascular disease including DR also showed a positive association with poorer COVID-19 outcomes including hospital admission and death.
- Further research is required, using more standardised methods to allow for direct comparison of results. If COVID-19 outcomes, DR identification, data collection and statistical analysis were common among studies, meta-analysis would be feasible which may reveal more accurate predictive power of DR and microvascular disease as clinically useful prognostic factors.

Keywords

Coronavirus, microvascular, microangiopathy, complications, risk factor

Abstract

Aims

Certain patients with Diabetes Mellitus (DM) have high risk for complications from COVID-19. We aimed to test the hypothesis that pre-existing diabetic retinopathy (DR), a microvascular disease, is a prognostic indicator for poor COVID-19 outcome in this heterogeneous population.

Methods

Seven databases (including MEDLINE) and grey literature were searched, identifying eligible studies using predetermined selection criteria. The Quality in Prognosis Studies (QUIPS) tool was used for quality assessment, followed by narrative synthesis of included studies.

Results

Eight cohort studies were identified. Three showed significant positive associations between DR and poor COVID-19 outcomes. The highest quality study, McGurnaghan, found increased risk of the combined outcome fatal or critical care unit (CCU)-treated COVID-19 with referable-grade DR (OR 1.672, 95% CI 1.38–2.03). Indirectly, four studies reported positive associations with microvascular disease and poorer prognosis. Variability between studies limited comparability.

Conclusions

The current literature suggests an independent association between DR and poorer COVID-19 prognosis in patients with DM after controlling for key variables such as age. The use of standardised methodology in future studies would establish the predictive value of DR with greater confidence. Researchers should consider comparing the predictive value of DR and its severity, to other microvascular complications of DM.

1. Introduction

Coronavirus Disease 2019 (COVID-19), caused by the SARS-CoV-2 virus, was initially identified in Wuhan, China on 2019/12/02. [1] Rapid global transmission of the virus resulted in the declaration of a pandemic by the World Health Organisation (WHO) on 2020/03/11. [2] By May 2021 WHO reported over 160 million confirmed cases and 3.3 million deaths.

Although the majority of those contracting COVID-19 suffer mild symptoms, there have been consistent reports of subgroups developing severe complications including acute respiratory distress syndrome (ARDS), resulting in intensive or critical care unit (ICU, CCU) admission or death. Poorer prognostic factors include age, sex and comorbidities (hypertension, cardiovascular disease and diabetes mellitus (DM)). [3]

WHO recently estimated global adult DM prevalence at 422 million. [4] Studies suggest DM doubles the relative risk of poor COVID-19 outcomes [5-7] and increases the risk of in-hospital death.[8] However, the microvascular impact of DM ranges from mild to severe and consequently there is substantial risk variation within this patient population. [9] Improving precision of risk stratification within the DM population would allow patients at risk to be identified.

Severe COVID-19 manifests in part as an extensive thromboembolic microvascular disease. [10, 11] This led to the hypothesis that people with diabetes with pre-existing microvascular disease may be more vulnerable **to the ensuing endothelitis resulting from COVID-19 infection and are thus more likely to suffer from adverse outcomes.** [10, 12, 13] **Microvascular disease reflects a more advanced diabetic status and** presents as diabetic retinopathy (DR), nephropathy or neuropathy in over a third of people newly diagnosed with Type 2 Diabetes Mellitus (T2DM). [10] DR may provide a useful index for systemic microvascular disease in the DM population as this information is relatively easy to acquire and is already collected by national screening programmes. [10]

We assessed the availability and quality of current evidence on the associations between DR and COVID-19. The primary objective was to determine whether pre-existing DR predicted poorer outcomes in patients with DM. We report calculated risks and relate this evidence to health policy and existing risk calculators, and ultimately recommend how future research could further improve the evidence-base.

2. Material and methods

We developed our protocol guided by PRISMA guidelines (ESM 1). [14] Eligibility criteria for included studies were based on the CHARMS checklist: [15]

- DM

- Confirmed COVID-19
- Non-interventional observational study design
- DR as prognostic factor (independently or with other microvascular diseases)
- Outcome including poor COVID-19 prognosis
- Comparison group without pre-existing DR.

Full details are provided in ESM 2.

2.1. Literature search

We carried out literature scoping between 2020/11/11-2021/01/31, and found no COVID-19 reviews in PROSPERO [16] with a focus on DR. An extensive literature search was carried out on 2021/06/16 for studies published since 2019/12/01, without language restrictions. The primary search strategy was established on MEDLINE (ESM 3). Two independent librarians (University of Edinburgh, British Medical Association) were consulted to maximise the balance of sensitivity and specificity. Studies identified during scoping as highly relevant to the research question were used to develop search precision via the Yale MeSH analyser. [17] The search was tested to determine whether it was sensitive enough to capture other known relevant studies which were poorly indexed by study design. The search was independently appraised with the PRESS 2015 checklist to ensure it had sufficient quality and relevance. [18]

We adapted the search syntax and structure to additional databases using the Polyglot tool (PubMed, Web of Science, Cochrane Reviews, EMBASE) and searched the Cochrane COVID-19 registry for unpublished studies. Grey literature databases, MedRxiv and the Global Index Medicus, were searched for literature not commercially published and in low to middle income countries. Additional searches were carried out via Diabetes UK and Diabetologica News. Complementary methods included forward and backward citation searching of studies that met the inclusion criteria. We did not conduct hand searching of journals. We used EndNote for bibliographic management.

2.2. Study selection

After deduplication, selection of studies involved two phases: abstract and full study screening. For studies without abstracts, criteria were applied to the title. In each stage, the lead author screened all studies and randomly split them for masked screening by one of two co-authors. Discrepancies were resolved by consensus.

2.3. Risk of bias assessment

Studies were assessed using the Quality of Prognosis Studies tool [19] covering six domains of potential bias: participation, attrition, prognostic factor measurement, outcome, confounding and analysis (ESM 4). [20] Assessment was conducted independently by two authors with discrepancies

resolved by consensus. No minimum quality bar was set; all which passed full screening were included. Bias assessments were incorporated, with studies at lower risk of bias weighted more heavily.

2.4. Data extraction

We used the CHARMS-PF checklist for data extraction. [19] Preliminary and final study results were included where relevant. For overlapping data, the final study was used. Where data were not reported in sufficient detail we attempted to request them from primary authors. We extracted study and participant characteristics, and strengths of association (odds ratios (OR) and hazard ratios (HR)), precision of results (95% CI) from univariate and multivariate analyses. Areas of heterogeneity between studies were noted as potential limitations. Results were given greater weighting where appropriate adjustments were made for confounding variables.

Data synthesis was narrative. Meta-analysis was considered unfeasible due to study heterogeneity.

3. Results

The PRISMA diagram (Figure 1) shows that the search generated a total of 376 studies after deduplication. Abstract and title screening excluded 331 studies, leaving 45 which were retrieved for full-text screening. Overall, eight studies met the selection criteria. [3, 9, 13, 21-25]

3.1. Study characteristics

Seven studies were from western Europe and one was from China [3] (Table 1). All were retrospective cohorts, measuring a series of prognostic factors for poor COVID-19 outcomes. The majority of included studies were conducted in the pandemic's first wave (2020/03–2020/07), one in the second wave (2020/09–2020/12) [24]. Patient characteristics were similar in terms of average age, ethnicity and sex and all had a diagnosis or medical history of DM. Most studies included a majority of patients with T2DM (88-100%), in one, only patients with T1DM [24]. One study included DM patients without COVID-19 in their comparison group. [9]

Wargny and its preliminary study (Cariou) are collectively known as the CORONADO studies. Cariou and Lasbleiz used a subset of patients in Wargny. Consequently, these three studies report outcomes from an overlapping patient population (shown in grey in tables). [21, 22, 25] Each study provided additional information by measuring different COVID-19 outcomes.

There were considerable differences between studies, primarily around outcome, DR identification, data collection, population size and statistical analysis. Only two studies used the same outcome (combined fatal/CCU admission). [9, 24] Crucially, DR identification varied between studies. Only one study compared the predictive value of different DR grades (non-referable and referable). [9] Others

included any [13], undefined [23, 24], or severe DR only [21, 22]. The three overlapping studies reported results for DR within the same group of microvascular diseases [21, 22, 25] One study reported results for DR captured within a broader group of diabetic complications. [23]

We report COVID-19 outcomes for subgroups of patients with and without DR as defined in each study. Between studies, the proportion of patients with known DR varied greatly, from 45% [24], 36% [13] and 24% [9] to <7% for the remaining studies. Two did not report detailed data for DR outwith their microvascular group, but relevant results are included for comparison. [23, 25]

Results from analyses (commonly univariate and/or multivariate logistic regression) are shown in Table 2. Thresholds for inclusion of variables into multivariate analysis varied, as did adjustment factors used. McGurnaghan did not perform univariate analysis; all variables were entered into multivariate analysis. Ruan also only conducted multivariate analysis (rationale for chosen variables not provided). Remaining studies, except Corcillo and Orioli, included variables with unadjusted $p < 0.05$ into multivariate analysis. Corcillo included variables with $p < 0.10$, Orioli those with unadjusted $p < 0.20$, together with backward elimination to introduce selected variables into multivariate analysis. Orioli and Wargny did not report group sizes for DR, however reported estimate of the effect of DR on their outcome. Where numbers of patients with DR with and without the study outcome were reported, odds ratios were calculated by review authors (Table 2).

3.2. Study quality

Due to this considerable heterogeneity between studies, results should be interpreted in the context of each study's characteristics and risk of bias (ESM 5). Overall, the major risks of bias were in outcome definition and prognostic factor identification. The studies were ranked as follows from highest to lowest reliability: McGurnaghan, Cariou, Wargny, Ruan, Corcillo, Orioli, Lasbleiz, and Zhang. The latter two had small numbers of DR patients ($n=14, 3$ respectively) so confidence in their analysis of DR as a prognostic factor was low.

Corcillo and Zhang had DR information on every patient, all others reported missing rates (**Error! Reference source not found.**). McGurnaghan used chained equations to impute missing data, assuming the data was missing at random. CORONADO studies used available data without imputation. Reasons for missing data were generally not reported but likely due to limitations of the retrospective study design and most studies made extensive effort to maximise data collection.

3.3. Diabetic retinopathy as a prognostic factor

Using multivariate logistic regression adjusted for age, sex, diabetes duration and diabetes type, McGurnaghan reported an association between clinically referable DR and fatal/CCU-treated COVID-19 (OR 1.67, 95% CI 1.38-2.03), but no association with non-referable DR (OR 1.16, 95% CI 0.98-1.38).

Cariou reported, through univariate analysis, an association between severe DR and death 7 days after admission (OR 2.05, 95% CI 1.03–4.07). However, despite significance in univariate analysis, severe DR was not included in subsequent multivariate analysis (reasons not provided). Microvascular disease was associated with death on day 7 in univariate analysis (OR 5.25, 95% CI 3.03-9.10) and in multivariate analysis, adjusted for age and sex (OR 2.14, 95% CI 1.16-3.94). Neither severe DR nor microvascular disease were significantly associated with the combined outcome of tracheal intubation and/or death <7 days after admission.

Ruan did not report univariate or multivariate analysis for DR but they did report outcomes for patients with and without DR, therefore an OR was calculated (OR 1.36 95% CI 0.68-2.70). They reported an association between microvascular disease and combined in-hospital death and/or ICU admission (OR 1.95, 95% 1.00-3.87) after adjusting for age. Microvascular disease was not associated with in-hospital death alone (OR 1.53, 95% CI 0.68-3.41).

Corcillo reported a non-significant univariate correlation ($R=0.13$, $p=0.090$) with DR and tracheal intubation. As above, for comparison, an OR was calculated based on reported numbers of patients with DR with/without the outcome (OR 1.68 95% CI 0.86-3.28). Despite this lack of association, DR was included in multivariate analysis, where DR was associated with tracheal intubation (OR 5.81, 95% CI 1.37–24.66). Adjustment variables were not reported. Unlike Cariou and Wargny, Corcillo found no association between DR and in-hospital death, however no data was provided to quantify this.

Orioli did not find an association between DR and in-hospital death in univariate analysis, with age and sex matched ($p = 0.655$). However, similarly to Corcillo, Orioli did not provide the group or effect size for DR to support this or to make inferences regarding the clinical relevance of effect size.

Lasbleiz reported an association between microvascular disease and hospital admission through a stepwise multivariate logistic regression analysis (OR 2.11, 95% CI 1.10-4.05). Zhang and Lasbleiz did not report associations between DR and their respective study outcomes.

Wargny, using a larger study population and longer duration of follow-up than the preliminary study by Cariou, did not report on DR independently, instead providing a collective microvascular disease definition. Microvascular disease (defined in Table 1) was associated with death <28 days after hospital admission (OR 2.11, 95% CI 1.35-3.27).

4. Discussion

This systematic review focussed on the pre-existence of DR as a predictor of poor COVID-19 outcomes. The evidence collated here is mixed, strongly reflecting the studies' variability around DR identification and outcomes. However, six of eight studies reported positive associations with pre-existing DR (or microvascular disease including DR) and poorer outcomes, thereby supporting a series of emerging scientific and clinical hypotheses around COVID-19. The two studies not reporting an association were the smallest ($n < 75$).

Whyte and Vas identified COVID-19 manifesting as a widespread microvascular disease in its more prolific form. [10, 12] Therefore it may be anticipated those with pre-existing microvascular disease would be more vulnerable to the ensuing additional endothelitis of COVID-19 infection. [26] Microangiopathy of the retina may reflect similar changes in less accessible organs, such as the lungs, kidney and heart. [27, 28] It has been suggested that microvascular disease impairs sufficient gas exchange, making the development of ARDS when infected with COVID-19 more likely. [29] As evidence emerged through the first year of the pandemic, commentary such as Corcillo's letter addressing McGurnaghan's findings and Scheen's short review of the Cariou study, emphasised the importance of any microvascular disease as a prognostic factor for poor COVID-19 prognosis in patients with diabetes. [30, 31] DR, the most easily measured microvascular disease is potentially useful for risk stratification in the diabetic population.

The review's most robust study found an association between referable (i.e. more severe) DR and fatal/ICU treated COVID-19, however, this promising evidence needs to be interpreted in context. [9] By including people with diabetes without COVID-19, unlike its counterparts, the study estimated the impact of DR on developing a severe COVID-19 outcome, comparing infected patients to a population in which the vast majority were not infected. The clinical relevance of such a comparison is not clear. Cariou found a correlation between severe DR and death by day seven of admission. However, although rated as second highest in study quality, the lack of adjustment in the analysis failed to establish whether there was any independent association over and above that of other risk factors. Corcillo did not find an association between DR and death but did report an association with tracheal intubation; the wide CI (1.37–24.66) reflecting their small sample size. The very small DR numbers in Lasbleiz and Zhang's studies may have led to the failure to detect an association with their outcome. [32] Orioli did not report a group size for DR, so the lack of a statistically significant effect size due to study design, rather than the lack of a true effect, cannot be ruled out.

The specific contribution of DR to outcomes within the collective microvascular disease group in the Cariou, Wargny, Ruan, Orioli and Lasbleiz studies cannot be determined, but this review's inclusion of all results for the impact of DR and microvascular disease on study outcomes may provide some insight. Ruan and the CORONADO studies found similar adjusted associations with death by day seven and day twenty-eight, death in hospital and/or ICU and chance of hospital admission. Unlike the CORONADO studies, Ruan did not find an association between in-hospital death and microvascular disease; the difference in patient populations in terms of T1DM and T2DM may have contributed to this. The lack of detail on time from Orioli and Ruan and the difference in outcome definitions makes comparison to the CORONADO studies less meaningful.

Renal disease, DM and DR could plausibly interact to cause poor COVID-19 outcomes. It may be that identifying generic microvascular disease (or nephropathy and neuropathy) is more predictive of poor COVID-19 outcomes than DR alone. Cariou, through univariate analysis, found a greater effect size for this microvascular disease group, with respect to death at day seven, than DR. Although not the focus of this review, Cariou reported a larger effect size (OR 3.19 95% CI 2.09-4.87) for diabetic nephropathy than severe DR (OR 2.05 95% CI 1.03-4.07) in univariate analysis for death on day 7. McGurnaghan had a slightly greater effect size for albuminuria than for referable DR at multivariate analysis. Additionally, both had larger sample sizes for nephropathy than for DR which may be due to nephropathy presenting earlier or that it is more commonly measured. As others have pointed out, the predictive value of nephropathy with COVID-19 death is consistent with the association with kidney disease and higher death rates in people with diabetes. [31] Overall, these results support the hypotheses that pre-existing microvascular disease increases the likelihood of poorer COVID-19 outcomes, however it was not clear that one microvascular disease had better prognostic value than another. DR, however, remains the most accessibly imaged microvascular disease and thus could provide the most effective risk stratification tool for clinicians.

Other accessible measurements, such as HbA1c, BMI and hypertension, are also potential prognostic factors for poor COVID-19 prognosis in the diabetic population. However, results from the most robust studies in this review, McGurnaghan, Wargny and Cariou, consistently reported DR and/or microvascular disease measured collectively as having a higher OR for poorer COVID-19 prognosis than the majority of these other measurements. With regards to death on day 7, Cariou reported an OR for microvascular disease (OR 5.25, 95% CI 3.03-9.10) and severe DR (OR 2.05, 95% CI 1.03-4.07) that was more than double the OR for BMI (OR 0.95, 95% CI 0.78-1.16) and diabetes duration (OR 1.01, 95% CI 0.99-1.04) and higher than the OR for dyslipidemia and hypertension. Furthermore, Wargny reported microvascular complications were associated with the highest OR for death within 28 days than any other accessible prognostic factor measured, including diabetes duration, type, HbA1c levels, BMI,

and ethnicity, hypertension and dyslipidemia. Moreover, with regards to CCU treated COVID-19, McGurnaghan reported the OR for referable retinopathy as higher than that for BMI, hypertension and total cholesterol. Regarding comparison to macrovascular diseases, Wargny reported a greater OR for microvascular disease. This was also the case regarding heart failure. However, McGurnaghan did not report an increased OR compared to existing heart diseases unlike Wargny and therefore this difference in association remains inconclusive. Overall, however, this evidence is supportive of the hypothesis that those with pre-existing microvascular disease are more at risk of poorer COVID-19 prognosis.

A growing body of evidence is leading to the conclusion that thrombo-inflammatory microvascular disease is a prominent feature of COVID-19 infection, especially amongst life-threatening cases. [10, 11] Therefore, it has been hypothesised that those with pre-existing microvascular disease are more vulnerable to this and therefore are more likely to suffer poorer COVID-19 prognosis. Although the overall pathophysiology for COVID-19, related to endothelial dysfunction, remains unclear, a working hypothesis suggests that endothelitis occurs from a combination of direct viral invasion and an imbalance within the Renin-Angiotensin system (RAAS) because of viral consumption of ACE-2. [11]

4.1. Limitations of results due to heterogeneity

Considerable variability between studies carried out early in a global pandemic is understandable, but it may also reflect the general lack of an established method for conducting and designing prognostic factor studies. This made it impractical to combine results and may explain some observed lack of replicability. [19] The major limitation to the body of evidence was the variability in outcome definition. Only McGurnaghan provided a rationale for their choice, stating that the combination of fatal/CCU-treated COVID-19 was appropriate, as hospitalisation depends on hospital policy and capacity, leading to observation bias.

The publication timeline also meant most studies reported very short-term outcomes, so the effect of DR and microvascular disease on Long Covid was not captured. Variability of outcomes is emerging as a common feature of COVID-19 literature. [33] Due to the need for rapid accumulation of data to guide appropriate responses to the pandemic, studies were organised quickly and conducted using varying methodology. However, reliable changes to clinical practice require reproducible and widely accepted outcomes to allow for efficient data sharing and pooling between studies. Consequently, the WHO have recommended a core set of outcome measures to define poor COVID-19 outcomes for future studies. These include death data collected up until 60 days or discharge, and the use of a WHO Clinical Progression Scale. [33]

Generalisability of hospital admission/discharge and death is limited as it is dependent on the availability of resources and so might vary between geographical areas, particularly when need overwhelms capacity. [9, 33] Moreover, tracheal intubation as an outcome is patient specific and largely contraindicated in the frail and elderly that contribute a large proportion of the population with poor COVID-19 outcomes. [21] Also, clinical management of patients changed as the pandemic progressed with the introduction of intravenous dexamethasone, remdesivir and tocilizumab, significantly decreasing requirement for mechanical ventilation. [34] Therefore, reproducing the results of the Corcillo or Cariou studies is likely unattainable.

To prevent confounding results, it is essential pre-existing DR is identified in patients prior to COVID-19 infection because emerging evidence suggests COVID-19 itself manifests as a DR. Screening programmes are an ideal data source. A series of case reports have shown signs of DR in patients with COVID-19 with no prior history of DR. [28, 35-38] Although evidence is limited to determine whether this is linked to poorer prognosis, it is still important to distinguish the two to prevent confounding the analysis. Unfortunately, this could only be confidently concluded in the McGurnaghan and Corcillo studies, due to their use of the prevalent annual UK DR screening program. Furthermore, data collection methods must be up to date to ensure patients with underlying DR are appropriately captured. Again, for the same reason, this could be confidently concluded from the McGurnaghan and Corcillo studies. For the remaining studies that relied on patient history and linked datasets, data completeness cannot be guaranteed.

Varying prevalence of DR amongst the study cohorts may be due to variability in data collection methods but is more likely due to variance in how DR was identified. Prevalence in the two total population studies in western Europe, McGurnaghan and Cariou, reflect the prevalence of DR in Europe for their respective DR definition with regards to T2DM. On average, 25.7% of people with T2DM in Europe have some degree of DR (prevalence in McGurnaghan: 24%) and 7.2% for severe DR (severe DR prevalence in Cariou: 5%). [39]

4.2. Clinical relevance

Despite some evidence of a positive association between DR and poor COVID-19 outcomes, it would be premature to propose changes to clinical practice from the existing literature. The inability to directly compare results and the relatively small heterogeneous evidence-base, precludes recommendations around change to current clinical practice. Future research is required to replicate and extend these findings to establish their validity.

Although the evidence suggested that other microvascular diseases such as nephropathy, were more strongly associated with poorer COVID-19 prognosis, DR is an accessible, informative index for systemic microvascular disease which could enhance risk stratification by clinicians. Moreover, DR (and microvascular disease in general) was consistently reported as being more greatly associated with poorer COVID-19 prognosis than other accessible measurements, such as HbA1c and BMI.

4.3. Review strengths and weaknesses

This systematic review used a comprehensive and inclusive methodology. The extensive literature search provided confidence we maximised relevant study inclusion. However, some studies were poorly indexed on databases and may not have been captured in the search. Furthermore, it is likely that further research has been published since completing this review. The use of masked dual selection, assessment and data extraction helped prevent selective reporting and biased decision making.

As noted, this systematic review could not incorporate a meta-analysis due to heterogeneity in study outcome and DR definition. It is therefore recommended future studies report internationally standardised definitions and outcomes and share raw data, to enable pooling, allowing greater power in results and more in-depth understanding. This will be a particular benefit to boost analysis around DR as studies with a small sample size may fail to find a real association which exists in the data.

4.4. Suggestions for future research

Prospective cohort studies would ensure better quality control over data collection. Studies should report unadjusted and adjusted estimates in their analyses and provide a biological (as well as statistical) rationale for the choice of their variables as plausible confounders.

Further work comparing the predictive value of different DR grades, like the McGurnaghan study, would greatly enhance the evidence. Most patients with DR tend to be categorised as mild, and the risk of complications is probably greatest for the minority who have severe DR, so detecting associations between DR and outcomes is highly likely to depend on its severity. It would be interesting to explore whether pre-existing DR is exacerbated by COVID-19 infection, and whether this is transient or prolonged. Further work to compare COVID-19 outcomes in T1DM and T2DM would be valuable.

Current literature is concentrated in Western Europe. Further international studies should be encouraged to assess outcomes in people with different ethnicities, healthcare systems and

socioeconomic environments. However, this may prove challenging, as up to date pre-existing DR classifications may be lacking, due to absent systematic DR screening programs in less affluent countries or those with under-funded healthcare systems. [40]

4.5. Conclusion

Current literature suggests a positive independent association between DR (independently or within microvascular disease) and poorer COVID-19 outcomes. However, the inability to directly compare the results of the studies limits confidence in the strength of this association. Future studies would add considerably to the evidence base by reporting standardised outcomes. Work is urgently needed by health organisations to explicitly define standard outcome measures for epidemiological work in the context of rapidly evolving public health emergencies such as the COVID-19 pandemic. Other microvascular diseases, particularly nephropathy, may have better predictive value than DR, however further research is warranted. Nonetheless, DR remains the most easily accessible diabetic microvascular disease to measure and may continue to play a key role as an efficient, objective, quantitative biomarker. Although demographic factors have played an important role in characterising severe COVID-19 risk and aid in the management of the pandemic, **microvascular disease may be more significant**. There is now an opportunity to refine risk estimates with patient data that may relate more closely to the mechanisms of disease. We believe that an index of microvascular health may be an important complementary tool for patient stratification and monitoring pathways.

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Conflict of Interest

The Authors declare no conflict of interest.

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PRE-EXISTING DIABETIC RETINOPATHY AS A PROGNOSTIC FACTOR FOR COVID-19 OUTCOMES AMONGST PEOPLE WITH DIABETES: A SYSTEMATIC REVIEW

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Highlights

- Severe diabetic retinopathy (DR) was independently associated with poorer outcomes of COVID-19, including need for critical care or death.
- Microvascular disease including DR also showed a positive association with poorer COVID-19 outcomes including hospital admission and death.
- Further research is required, using more standardised methods to allow for direct comparison of results. If COVID-19 outcomes, DR identification, data collection and statistical analysis were common among studies, meta-analysis would be feasible which may reveal more accurate predictive power of DR and microvascular disease as clinically useful prognostic factors.

Keywords

Coronavirus, microvascular, microangiopathy, complications, risk factor

Abstract

Aims

Certain patients with Diabetes Mellitus (DM) have high risk for complications from COVID-19. We aimed to test the hypothesis that pre-existing diabetic retinopathy (DR), a microvascular disease, is a prognostic indicator for poor COVID-19 outcome in this heterogeneous population.

Methods

Seven databases (including MEDLINE) and grey literature were searched, identifying eligible studies using predetermined selection criteria. The Quality in Prognosis Studies (QUIPS) tool was used for quality assessment, followed by narrative synthesis of included studies.

Results

Eight cohort studies were identified. Three showed significant positive associations between DR and poor COVID-19 outcomes. The highest quality study, McGurnaghan, found increased risk of the combined outcome fatal or critical care unit (CCU)-treated COVID-19 with referable-grade DR (OR 1.672, 95% CI 1.38–2.03). Indirectly, four studies reported positive associations with microvascular disease and poorer prognosis. Variability between studies limited comparability.

Conclusions

The current literature suggests an independent association between DR and poorer COVID-19 prognosis in patients with DM after controlling for key variables such as age. The use of standardised methodology in future studies would establish the predictive value of DR with greater confidence. Researchers should consider comparing the predictive value of DR and its severity, to other microvascular complications of DM.

1. Introduction

Coronavirus Disease 2019 (COVID-19), caused by the SARS-CoV-2 virus, was initially identified in Wuhan, China on 2019/12/02. [1] Rapid global transmission of the virus resulted in the declaration of a pandemic by the World Health Organisation (WHO) on 2020/03/11. [2] By May 2021 WHO reported over 160 million confirmed cases and 3.3 million deaths.

Although the majority of those contracting COVID-19 suffer mild symptoms, there have been consistent reports of subgroups developing severe complications including acute respiratory distress syndrome (ARDS), resulting in intensive or critical care unit (ICU, CCU) admission or death. Poorer prognostic factors include age, sex and comorbidities (hypertension, cardiovascular disease and diabetes mellitus (DM)). [3]

WHO recently estimated global adult DM prevalence at 422 million. [4] Studies suggest DM doubles the relative risk of poor COVID-19 outcomes [5-7] and increases the risk of in-hospital death.[8] However, the microvascular impact of DM ranges from mild to severe and consequently there is substantial risk variation within this patient population. [9] Improving precision of risk stratification within the DM population would allow patients at risk to be identified.

Severe COVID-19 manifests in part as an extensive thromboembolic microvascular disease. [10, 11] This led to the hypothesis that people with diabetes with pre-existing microvascular disease may be more vulnerable to the ensuing endothelitis resulting from COVID-19 infection and are thus more likely to suffer from adverse outcomes. [10, 12, 13] Microvascular disease reflects a more advanced diabetic status and presents as diabetic retinopathy (DR), nephropathy or neuropathy in over a third of people newly diagnosed with Type 2 Diabetes Mellitus (T2DM). [10] DR may provide a useful index for systemic microvascular disease in the DM population as this information is relatively easy to acquire and is already collected by national screening programmes. [10]

We assessed the availability and quality of current evidence on the associations between DR and COVID-19. The primary objective was to determine whether pre-existing DR predicted poorer outcomes in patients with DM. We report calculated risks and relate this evidence to health policy and existing risk calculators, and ultimately recommend how future research could further improve the evidence-base.

2. Material and methods

We developed our protocol guided by PRISMA guidelines (ESM 1). [14] Eligibility criteria for included studies were based on the CHARMS checklist: [15]

- DM

- Confirmed COVID-19
- Non-interventional observational study design
- DR as prognostic factor (independently or with other microvascular diseases)
- Outcome including poor COVID-19 prognosis
- Comparison group without pre-existing DR.

Full details are provided in ESM 2.

2.1. Literature search

We carried out literature scoping between 2020/11/11-2021/01/31, and found no COVID-19 reviews in PROSPERO [16] with a focus on DR. An extensive literature search was carried out on 2021/06/16 for studies published since 2019/12/01, without language restrictions. The primary search strategy was established on MEDLINE (ESM 3). Two independent librarians (University of Edinburgh, British Medical Association) were consulted to maximise the balance of sensitivity and specificity. Studies identified during scoping as highly relevant to the research question were used to develop search precision via the Yale MeSH analyser. [17] The search was tested to determine whether it was sensitive enough to capture other known relevant studies which were poorly indexed by study design. The search was independently appraised with the PRESS 2015 checklist to ensure it had sufficient quality and relevance. [18]

We adapted the search syntax and structure to additional databases using the Polyglot tool (PubMed, Web of Science, Cochrane Reviews, EMBASE) and searched the Cochrane COVID-19 registry for unpublished studies. Grey literature databases, MedRxiv and the Global Index Medicus, were searched for literature not commercially published and in low to middle income countries. Additional searches were carried out via Diabetes UK and Diabetologica News. Complementary methods included forward and backward citation searching of studies that met the inclusion criteria. We did not conduct hand searching of journals. We used EndNote for bibliographic management.

2.2. Study selection

After deduplication, selection of studies involved two phases: abstract and full study screening. For studies without abstracts, criteria were applied to the title. In each stage, the lead author screened all studies and randomly split them for masked screening by one of two co-authors. Discrepancies were resolved by consensus.

2.3. Risk of bias assessment

Studies were assessed using the Quality of Prognosis Studies tool [19] covering six domains of potential bias: participation, attrition, prognostic factor measurement, outcome, confounding and analysis (ESM 4). [20] Assessment was conducted independently by two authors with discrepancies

resolved by consensus. No minimum quality bar was set; all which passed full screening were included. Bias assessments were incorporated, with studies at lower risk of bias weighted more heavily.

2.4. Data extraction

We used the CHARMS-PF checklist for data extraction. [19] Preliminary and final study results were included where relevant. For overlapping data, the final study was used. Where data were not reported in sufficient detail we attempted to request them from primary authors. We extracted study and participant characteristics, and strengths of association (odds ratios (OR) and hazard ratios (HR)), precision of results (95% CI) from univariate and multivariate analyses. Areas of heterogeneity between studies were noted as potential limitations. Results were given greater weighting where appropriate adjustments were made for confounding variables.

Data synthesis was narrative. Meta-analysis was considered unfeasible due to study heterogeneity.

3. Results

The PRISMA diagram (Figure 1) shows that the search generated a total of 376 studies after deduplication. Abstract and title screening excluded 331 studies, leaving 45 which were retrieved for full-text screening. Overall, eight studies met the selection criteria. [3, 9, 13, 21-25]

3.1. Study characteristics

Seven studies were from western Europe and one was from China [3] (Table 1). All were retrospective cohorts, measuring a series of prognostic factors for poor COVID-19 outcomes. The majority of included studies were conducted in the pandemic's first wave (2020/03–2020/07), one in the second wave (2020/09–2020/12) [24]. Patient characteristics were similar in terms of average age, ethnicity and sex and all had a diagnosis or medical history of DM. Most studies included a majority of patients with T2DM (88-100%), in one, only patients with T1DM [24]. One study included DM patients without COVID-19 in their comparison group. [9]

Wargny and its preliminary study (Cariou) are collectively known as the CORONADO studies. Cariou and Lasbleiz used a subset of patients in Wargny. Consequently, these three studies report outcomes from an overlapping patient population (shown in grey in tables). [21, 22, 25] Each study provided additional information by measuring different COVID-19 outcomes.

There were considerable differences between studies, primarily around outcome, DR identification, data collection, population size and statistical analysis. Only two studies used the same outcome (combined fatal/CCU admission). [9, 24] Crucially, DR identification varied between studies. Only one study compared the predictive value of different DR grades (non-referable and referable). [9] Others

included any [13], undefined [23, 24], or severe DR only [21, 22]. The three overlapping studies reported results for DR within the same group of microvascular diseases [21, 22, 25] One study reported results for DR captured within a broader group of diabetic complications. [23]

We report COVID-19 outcomes for subgroups of patients with and without DR as defined in each study. Between studies, the proportion of patients with known DR varied greatly, from 45% [24], 36% [13] and 24% [9] to <7% for the remaining studies. Two did not report detailed data for DR outwith their microvascular group, but relevant results are included for comparison. [23, 25]

Results from analyses (commonly univariate and/or multivariate logistic regression) are shown in Table 2. Thresholds for inclusion of variables into multivariate analysis varied, as did adjustment factors used. McGurnaghan did not perform univariate analysis; all variables were entered into multivariate analysis. Ruan also only conducted multivariate analysis (rationale for chosen variables not provided). Remaining studies, except Corcillo and Orioli, included variables with unadjusted $p < 0.05$ into multivariate analysis. Corcillo included variables with $p < 0.10$, Orioli those with unadjusted $p < 0.20$, together with backward elimination to introduce selected variables into multivariate analysis. Orioli and Wargny did not report group sizes for DR, however reported estimate of the effect of DR on their outcome. Where numbers of patients with DR with and without the study outcome were reported, odds ratios were calculated by review authors (Table 2).

3.2. Study quality

Due to this considerable heterogeneity between studies, results should be interpreted in the context of each study's characteristics and risk of bias (ESM 5). Overall, the major risks of bias were in outcome definition and prognostic factor identification. The studies were ranked as follows from highest to lowest reliability: McGurnaghan, Cariou, Wargny, Ruan, Corcillo, Orioli, Lasbleiz, and Zhang. The latter two had small numbers of DR patients ($n=14, 3$ respectively) so confidence in their analysis of DR as a prognostic factor was low.

Corcillo and Zhang had DR information on every patient, all others reported missing rates (**Error! Reference source not found.**). McGurnaghan used chained equations to impute missing data, assuming the data was missing at random. CORONADO studies used available data without imputation. Reasons for missing data were generally not reported but likely due to limitations of the retrospective study design and most studies made extensive effort to maximise data collection.

3.3. Diabetic retinopathy as a prognostic factor

Using multivariate logistic regression adjusted for age, sex, diabetes duration and diabetes type, McGurnaghan reported an association between clinically referable DR and fatal/CCU-treated COVID-19 (OR 1.67, 95% CI 1.38-2.03), but no association with non-referable DR (OR 1.16, 95% CI 0.98-1.38).

Cariou reported, through univariate analysis, an association between severe DR and death 7 days after admission (OR 2.05, 95% CI 1.03–4.07). However, despite significance in univariate analysis, severe DR was not included in subsequent multivariate analysis (reasons not provided). Microvascular disease was associated with death on day 7 in univariate analysis (OR 5.25, 95% CI 3.03-9.10) and in multivariate analysis, adjusted for age and sex (OR 2.14, 95% CI 1.16-3.94). Neither severe DR nor microvascular disease were significantly associated with the combined outcome of tracheal intubation and/or death <7 days after admission.

Ruan did not report univariate or multivariate analysis for DR but they did report outcomes for patients with and without DR, therefore an OR was calculated (OR 1.36 95% CI 0.68-2.70). They reported an association between microvascular disease and combined in-hospital death and/or ICU admission (OR 1.95, 95% 1.00-3.87) after adjusting for age. Microvascular disease was not associated with in-hospital death alone (OR 1.53, 95% CI 0.68-3.41).

Corcillo reported a non-significant univariate correlation ($R=0.13$, $p=0.090$) with DR and tracheal intubation. As above, for comparison, an OR was calculated based on reported numbers of patients with DR with/without the outcome (OR 1.68 95% CI 0.86-3.28). Despite this lack of association, DR was included in multivariate analysis, where DR was associated with tracheal intubation (OR 5.81, 95% CI 1.37–24.66). Adjustment variables were not reported. Unlike Cariou and Wargny, Corcillo found no association between DR and in-hospital death, however no data was provided to quantify this.

Orioli did not find an association between DR and in-hospital death in univariate analysis, with age and sex matched ($p = 0.655$). However, similarly to Corcillo, Orioli did not provide the group or effect size for DR to support this or to make inferences regarding the clinical relevance of effect size.

Lasbleiz reported an association between microvascular disease and hospital admission through a stepwise multivariate logistic regression analysis (OR 2.11, 95% CI 1.10-4.05). Zhang and Lasbleiz did not report associations between DR and their respective study outcomes.

Wargny, using a larger study population and longer duration of follow-up than the preliminary study by Cariou, did not report on DR independently, instead providing a collective microvascular disease definition. Microvascular disease (defined in Table 1) was associated with death <28 days after hospital admission (OR 2.11, 95% CI 1.35-3.27).

4. Discussion

This systematic review focussed on the pre-existence of DR as a predictor of poor COVID-19 outcomes. The evidence collated here is mixed, strongly reflecting the studies' variability around DR identification and outcomes. However, six of eight studies reported positive associations with pre-existing DR (or microvascular disease including DR) and poorer outcomes, thereby supporting a series of emerging scientific and clinical hypotheses around COVID-19. The two studies not reporting an association were the smallest ($n < 75$).

Whyte and Vas identified COVID-19 manifesting as a widespread microvascular disease in its more prolific form. [10, 12] Therefore it may be anticipated those with pre-existing microvascular disease would be more vulnerable to the ensuing additional endothelitis of COVID-19 infection. [26] Microangiopathy of the retina may reflect similar changes in less accessible organs, such as the lungs, kidney and heart. [27, 28] It has been suggested that microvascular disease impairs sufficient gas exchange, making the development of ARDS when infected with COVID-19 more likely. [29] As evidence emerged through the first year of the pandemic, commentary such as Corcillo's letter addressing McGurnaghan's findings and Scheen's short review of the Cariou study, emphasised the importance of any microvascular disease as a prognostic factor for poor COVID-19 prognosis in patients with diabetes. [30, 31] DR, the most easily measured microvascular disease is potentially useful for risk stratification in the diabetic population.

The review's most robust study found an association between referable (i.e. more severe) DR and fatal/ICU treated COVID-19, however, this promising evidence needs to be interpreted in context. [9] By including people with diabetes without COVID-19, unlike its counterparts, the study estimated the impact of DR on developing a severe COVID-19 outcome, comparing infected patients to a population in which the vast majority were not infected. The clinical relevance of such a comparison is not clear. Cariou found a correlation between severe DR and death by day seven of admission. However, although rated as second highest in study quality, the lack of adjustment in the analysis failed to establish whether there was any independent association over and above that of other risk factors. Corcillo did not find an association between DR and death but did report an association with tracheal intubation; the wide CI (1.37–24.66) reflecting their small sample size. The very small DR numbers in Lasbleiz and Zhang's studies may have led to the failure to detect an association with their outcome. [32] Orioli did not report a group size for DR, so the lack of a statistically significant effect size due to study design, rather than the lack of a true effect, cannot be ruled out.

The specific contribution of DR to outcomes within the collective microvascular disease group in the Cariou, Wargny, Ruan, Orioli and Lasbleiz studies cannot be determined, but this review's inclusion of all results for the impact of DR and microvascular disease on study outcomes may provide some insight. Ruan and the CORONADO studies found similar adjusted associations with death by day seven and day twenty-eight, death in hospital and/or ICU and chance of hospital admission. Unlike the CORONADO studies, Ruan did not find an association between in-hospital death and microvascular disease; the difference in patient populations in terms of T1DM and T2DM may have contributed to this. The lack of detail on time from Orioli and Ruan and the difference in outcome definitions makes comparison to the CORONADO studies less meaningful.

Renal disease, DM and DR could plausibly interact to cause poor COVID-19 outcomes. It may be that identifying generic microvascular disease (or nephropathy and neuropathy) is more predictive of poor COVID-19 outcomes than DR alone. Cariou, through univariate analysis, found a greater effect size for this microvascular disease group, with respect to death at day seven, than DR. Although not the focus of this review, Cariou reported a larger effect size (OR 3.19, 95% CI 2.09-4.87) for diabetic nephropathy than severe DR (OR 2.05, 95% CI 1.03-4.07) in univariate analysis for death on day 7. McGurnaghan had a slightly greater effect size for albuminuria than for referable DR at multivariate analysis. Additionally, both had larger sample sizes for nephropathy than for DR which may be due to nephropathy presenting earlier or that it is more commonly measured. As others have pointed out, the predictive value of nephropathy with COVID-19 death is consistent with the association with kidney disease and higher death rates in people with diabetes. [31] Overall, these results support the hypotheses that pre-existing microvascular disease increases the likelihood of poorer COVID-19 outcomes, however it was not clear that one microvascular disease had better prognostic value than another. DR, however, remains the most accessibly imaged microvascular disease and thus could provide the most effective risk stratification tool for clinicians.

Other accessible measurements, such as HbA1c, BMI and hypertension, are also potential prognostic factors for poor COVID-19 prognosis in the diabetic population. However, results from the most robust studies in this review, McGurnaghan, Wargny and Cariou, consistently reported DR and/or microvascular disease measured collectively as having a higher OR for poorer COVID-19 prognosis than the majority of these other measurements. With regards to death on day 7, Cariou reported an OR for microvascular disease (OR 5.25, 95% CI 3.03-9.10) and severe DR (OR 2.05, 95% CI 1.03-4.07) that was more than double the OR for BMI (OR 0.95, 95% CI 0.78-1.16) and diabetes duration (OR 1.01, 95% CI 0.99-1.04) and higher than the OR for dyslipidemia and hypertension. Furthermore, Wargny reported microvascular complications were associated with the highest OR for death within 28 days than any other accessible prognostic factor measured, including diabetes duration, type, HbA1c levels, BMI,

and ethnicity, hypertension and dyslipidemia. Moreover, with regards to CCU treated COVID-19, McGurnaghan reported the OR for referable retinopathy as higher than that for BMI, hypertension and total cholesterol. Regarding comparison to macrovascular diseases, Wargny reported a greater OR for microvascular disease. This was also the case regarding heart failure. However, McGurnaghan did not report an increased OR compared to existing heart diseases unlike Wargny and therefore this difference in association remains inconclusive. Overall, however, this evidence is supportive of the hypothesis that those with pre-existing microvascular disease are more at risk of poorer COVID-19 prognosis.

A growing body of evidence is leading to the conclusion that thrombo-inflammatory microvascular disease is a prominent feature of COVID-19 infection, especially amongst life-threatening cases. [10, 11] Therefore, it has been hypothesised that those with pre-existing microvascular disease are more vulnerable to this and therefore are more likely to suffer poorer COVID-19 prognosis. Although the overall pathophysiology for COVID-19, related to endothelial dysfunction, remains unclear, a working hypothesis suggests that endothelitis occurs from a combination of direct viral invasion and an imbalance within the Renin-Angiotensin system (RAAS) because of viral consumption of ACE-2. [11]

4.1. Limitations of results due to heterogeneity

Considerable variability between studies carried out early in a global pandemic is understandable, but it may also reflect the general lack of an established method for conducting and designing prognostic factor studies. This made it impractical to combine results and may explain some observed lack of replicability. [19] The major limitation to the body of evidence was the variability in outcome definition. Only McGurnaghan provided a rationale for their choice, stating that the combination of fatal/CCU-treated COVID-19 was appropriate, as hospitalisation depends on hospital policy and capacity, leading to observation bias.

The publication timeline also meant most studies reported very short-term outcomes, so the effect of DR and microvascular disease on Long Covid was not captured. Variability of outcomes is emerging as a common feature of COVID-19 literature. [33] Due to the need for rapid accumulation of data to guide appropriate responses to the pandemic, studies were organised quickly and conducted using varying methodology. However, reliable changes to clinical practice require reproducible and widely accepted outcomes to allow for efficient data sharing and pooling between studies. Consequently, the WHO have recommended a core set of outcome measures to define poor COVID-19 outcomes for future studies. These include death data collected up until 60 days or discharge, and the use of a WHO Clinical Progression Scale. [33]

Generalisability of hospital admission/discharge and death is limited as it is dependent on the availability of resources and so might vary between geographical areas, particularly when need overwhelms capacity. [9, 33] Moreover, tracheal intubation as an outcome is patient specific and largely contraindicated in the frail and elderly that contribute a large proportion of the population with poor COVID-19 outcomes. [21] Also, clinical management of patients changed as the pandemic progressed with the introduction of intravenous dexamethasone, remdesivir and tocilizumab, significantly decreasing requirement for mechanical ventilation. [34] Therefore, reproducing the results of the Corcillo or Cariou studies is likely unattainable.

To prevent confounding results, it is essential pre-existing DR is identified in patients prior to COVID-19 infection because emerging evidence suggests COVID-19 itself manifests as a DR. Screening programmes are an ideal data source. A series of case reports have shown signs of DR in patients with COVID-19 with no prior history of DR. [28, 35-38] Although evidence is limited to determine whether this is linked to poorer prognosis, it is still important to distinguish the two to prevent confounding the analysis. Unfortunately, this could only be confidently concluded in the McGurnaghan and Corcillo studies, due to their use of the prevalent annual UK DR screening program. Furthermore, data collection methods must be up to date to ensure patients with underlying DR are appropriately captured. Again, for the same reason, this could be confidently concluded from the McGurnaghan and Corcillo studies. For the remaining studies that relied on patient history and linked datasets, data completeness cannot be guaranteed.

Varying prevalence of DR amongst the study cohorts may be due to variability in data collection methods but is more likely due to variance in how DR was identified. Prevalence in the two total population studies in western Europe, McGurnaghan and Cariou, reflect the prevalence of DR in Europe for their respective DR definition with regards to T2DM. On average, 25.7% of people with T2DM in Europe have some degree of DR (prevalence in McGurnaghan: 24%) and 7.2% for severe DR (severe DR prevalence in Cariou: 5%). [39]

4.2. Clinical relevance

Despite some evidence of a positive association between DR and poor COVID-19 outcomes, it would be premature to propose changes to clinical practice from the existing literature. The inability to directly compare results and the relatively small heterogeneous evidence-base, precludes recommendations around change to current clinical practice. Future research is required to replicate and extend these findings to establish their validity.

Although the evidence suggested that other microvascular diseases such as nephropathy, were more strongly associated with poorer COVID-19 prognosis, DR is an accessible, informative index for systemic microvascular disease which could enhance risk stratification by clinicians. Moreover, DR (and microvascular disease in general) was consistently reported as being more greatly associated with poorer COVID-19 prognosis than other accessible measurements, such as HbA1c and BMI.

4.3. Review strengths and weaknesses

This systematic review used a comprehensive and inclusive methodology. The extensive literature search provided confidence we maximised relevant study inclusion. However, some studies were poorly indexed on databases and may not have been captured in the search. Furthermore, it is likely that further research has been published since completing this review. The use of masked dual selection, assessment and data extraction helped prevent selective reporting and biased decision making.

As noted, this systematic review could not incorporate a meta-analysis due to heterogeneity in study outcome and DR definition. It is therefore recommended future studies report internationally standardised definitions and outcomes and share raw data, to enable pooling, allowing greater power in results and more in-depth understanding. This will be a particular benefit to boost analysis around DR as studies with a small sample size may fail to find a real association which exists in the data.

4.4. Suggestions for future research

Prospective cohort studies would ensure better quality control over data collection. Studies should report unadjusted and adjusted estimates in their analyses and provide a biological (as well as statistical) rationale for the choice of their variables as plausible confounders.

Further work comparing the predictive value of different DR grades, like the McGurnaghan study, would greatly enhance the evidence. Most patients with DR tend to be categorised as mild, and the risk of complications is probably greatest for the minority who have severe DR, so detecting associations between DR and outcomes is highly likely to depend on its severity. It would be interesting to explore whether pre-existing DR is exacerbated by COVID-19 infection, and whether this is transient or prolonged. Further work to compare COVID-19 outcomes in T1DM and T2DM would be valuable.

Current literature is concentrated in Western Europe. Further international studies should be encouraged to assess outcomes in people with different ethnicities, healthcare systems and

socioeconomic environments. However, this may prove challenging, as up to date pre-existing DR classifications may be lacking, due to absent systematic DR screening programs in less affluent countries or those with under-funded healthcare systems. [40]

4.5. Conclusion

Current literature suggests a positive independent association between DR (independently or within microvascular disease) and poorer COVID-19 outcomes. However, the inability to directly compare the results of the studies limits confidence in the strength of this association. Future studies would add considerably to the evidence base by reporting standardised outcomes. Work is urgently needed by health organisations to explicitly define standard outcome measures for epidemiological work in the context of rapidly evolving public health emergencies such as the COVID-19 pandemic. Other microvascular diseases, particularly nephropathy, may have better predictive value than DR, however further research is warranted. Nonetheless, DR remains the most easily accessible diabetic microvascular disease to measure and may continue to play a key role as an efficient, objective, quantitative biomarker. Although demographic factors have played an important role in characterising severe COVID-19 risk and aid in the management of the pandemic, microvascular disease may be more significant. There is now an opportunity to refine risk estimates with patient data that may relate more closely to the mechanisms of disease. We believe that an index of microvascular health may be an important complementary tool for patient stratification and monitoring pathways.

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Conflict of Interest

The Authors declare no conflict of interest.

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Figure 1. PRISMA flow diagram showing results of the literature search.

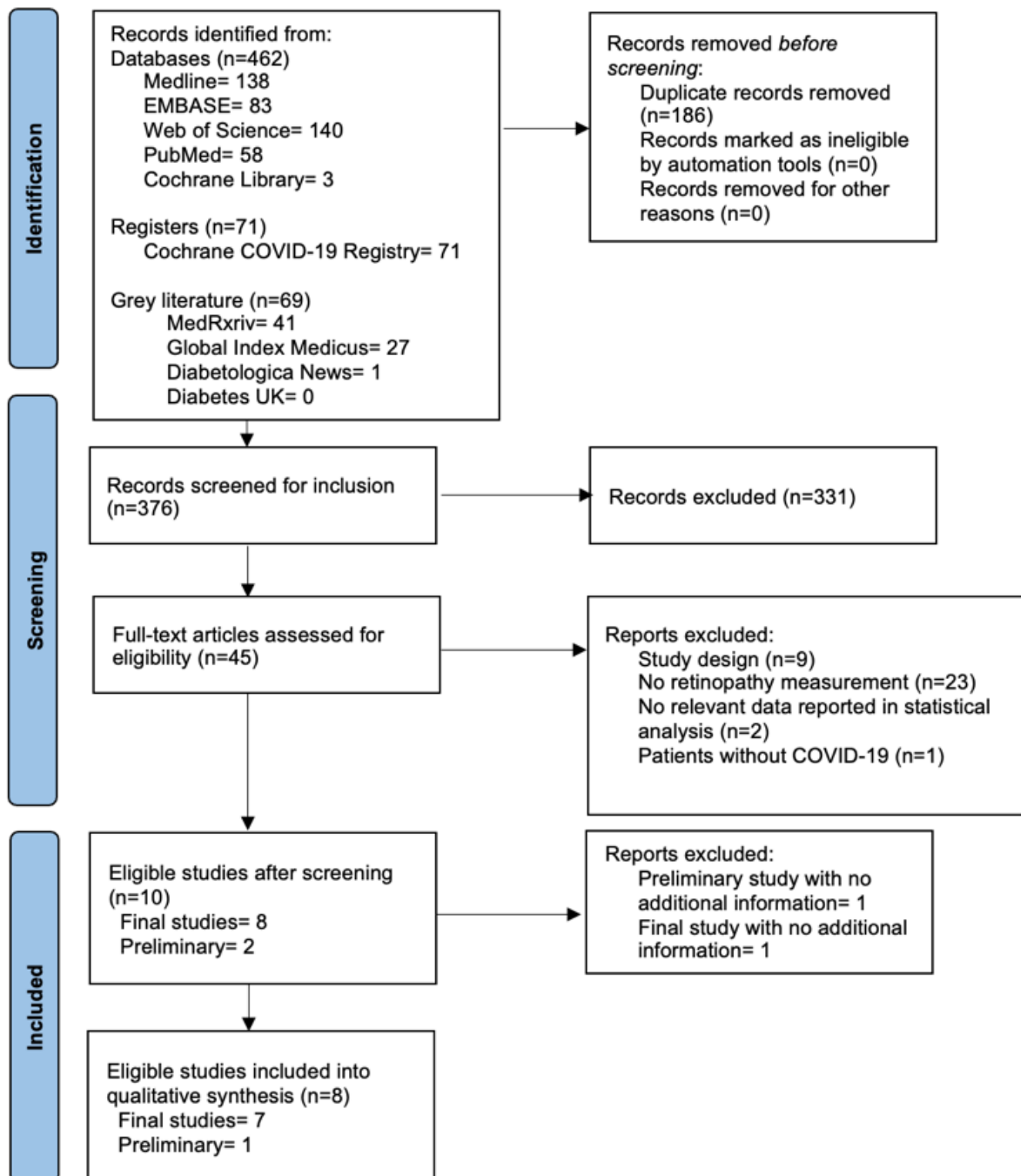


Table 1. Study characteristics and definitions. Grey studies based on overlapping patient populations.

Study [ref] (1 st /2 nd pandemic wave)	Study population, n		DR		Patient characteristics					Relevant outcomes
	DM + COVID-19	DM	Identification	Source	Sex, % female	Mean age	T2DM %	Ethnicity %	DR, n of data available (%)	
Cariou, France [21] (1 st)	1,317		<ul style="list-style-type: none"> Severe DR¹ Microvascular disease² 	Patient history, contact with medical professionals	36.5	65	88.5	white 61.9, black 35.7, asian 2.3	66 of 954 (7%)	<ul style="list-style-type: none"> Tracheal intubation or death <7 days after admission Death on day 7
Corcillo, England UK [13] (1 st)	187		<ul style="list-style-type: none"> DR (any) 	Annual screening	40	67	89	white 39, black 44, asian 8	67 of 187 (36%)	<ul style="list-style-type: none"> Tracheal intubation Death after hospital admission
Lasbleiz, France [22] (1 st)	334		<ul style="list-style-type: none"> Severe DR¹ Microvascular disease² 	Patient history, contact with medical professionals	59.3	62.1	94.2	white 35.3, black 64, asian 0.7	14 of 294 (5%)	<ul style="list-style-type: none"> Hospital admission
McGurnaghan, Scotland UK [9] (1 st)		319,349	<ul style="list-style-type: none"> Non-referable / referable DR³ 	Annual screening	59.3	62.1	86.4	white 74.5, black 0.5, asian 2.9	77,088 of 316,284 (24%)	<ul style="list-style-type: none"> Death or CCU admission
Ruan, England UK [24] (2 nd)	196		<ul style="list-style-type: none"> DR Microvascular disease⁴ 	Nationwide audit medical records	40	68	0	white 70, black 8, asian 13	63 of 139 (45%)	<ul style="list-style-type: none"> In-hospital death or ICU admission Death
Zhang, Wuhan China [3] (1 st)	52		<ul style="list-style-type: none"> DR (any) 	Patient history	36.5	65	100	Not reported	3 of 52 (6%)	<ul style="list-style-type: none"> ICU admission, mechanical ventilation or death
DR patient numbers not reported separately										

¹ proliferative retinopathy and/or laser photocoagulation and/or clinically significant macular oedema requiring laser and/or intra-vitreal injections

² severe DR and/or diabetic kidney disease (proteinuria [AER ≥300 mg/24 h; urinary albumin/creatinine ratio ≥300 mg/g; urinary albumin/creatinine ratio ≥30 mg/mmol creatinine; proteinuria ≥500 mg/24 h] and/or eGFR equal to or lower than 60 mL/min/1.73 m⁻², using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula) and/or history of diabetic foot ulcer

³ Feature-based grading

⁴ diabetic foot ulcer, diabetic nephropathy, diabetic peripheral neuropathy and DR

Orioli, Belgium [23] (1 st)	73		<ul style="list-style-type: none"> • Diabetic complications⁵ 	Institutional registry, electronic medical records	59.3	62.1	94.2	white 79.5, black 16.4, asian 4.1	39 of 66 (59%) microvascular disease	<ul style="list-style-type: none"> • In-hospital death
Wargny, France [25] (1 st)	2,796		<ul style="list-style-type: none"> • Microvascular disease⁶ 	Patient history, contact with medical professionals	36.3	69.7	88.2	white 56.2, black 40.2, asian 3.5	869 of 1,966 (44%) microvascular disease)	<ul style="list-style-type: none"> • Death <28 days after admission

⁵ DR, nephropathy, neuropathy, foot ulcer, and ischemic heart disease, peripheral arterial disease, ischemic cerebrovascular disease

⁶ diabetic kidney disease and/or severe DR and/or diabetic foot ulcer

Table 1. Results of relevant uni- & multivariate analysis reported by each study, or calculated by the review authors based on reported number of patients with DR with/without the study outcome – indicated by subscript. Grey indicates studies based on overlapping patient populations. Green text highlights statistically significant associations.

Author	DR identification	Outcome	Univariate analysis OR (95% CI)	P Value	Multivariate analysis OR (95% CI)	P value
Cariou [21]	Severe DR	Tracheal intubation or death <7 days after admission	1.22 (0.71, 2.11)	0.47		
	Microvascular disease		1.28 (0.94, 1.73)	0.11		
	Severe DR	Death on day 7	2.05 (1.03,4.07)	0.04		
	Microvascular disease		5.25 (3.03,9.10)	<0.0001	2.14 (1.16,3.94)	0.015
Corcillo [13]	DR	Tracheal intubation	<i>[1.68 (0.86-3.28)]¹</i>	<i>[0.125]⁷</i>	5.81 (1.37-24.66)	<0.001
		Death after admission			No association ²	Not reported
Lasbleiz [22]	Severe DR	Hospital admission	<i>[1.23 (0.42-3.61)]⁷</i>	<i>[0.71]⁷</i>		
	Microvascular disease		Not reported	<0.001	2.11 (1.10, 4.05)	0.02
McGurnaghan [9]	Non-referable DR	Death or CCU admission			1.16 (0.98-1.38)	0.094
	Referable DR				1.67 (1.38-2.03)	<0.001
Orioli [23]	DR	In-hospital death	Not reported	0.655		
Ruan [24]	DR	In-hospital death or ICU admission	<i>[1.36 (0.68-2.70)]⁷</i>	<i>[0.378]⁷</i>		
	Microvascular disease	In-hospital death or ICU admission			1.95 (1.00-3.97)	0.05
		Death				1.53 (0.68-3.41)
Zhang [3]	DR	ICU admission, mechanical ventilation or death	<i>[3.04 (0.15-61.4)]⁷</i>	<i>[0.49]⁷</i>		
DR results not reported separately						
Wargny [25]	Microvascular disease	Death <28 days after admission	3.94 (3.08, 5.03)	Not reported	2.11 (1.35-3.27)	0.031

¹ [odds ratio & confidence interval calculated by review authors using reported numbers of patients with/without DR who did and didn't have the outcome]

² "No association" reported, but without detail



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