The Impact of CKD Anaemia on Patients: Incidence, Risk Factors, and Clinical Outcomes—A Systematic Literature Review

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Anaemia is a common consequence of chronic kidney disease (CKD); however, the risk factors for its development and its impact on outcomes have not been well synthesised. Therefore, we undertook a systematic review to fully characterise the risk factors associated with the presence of anaemia in patients with CKD and a contemporary synthesis of the risks of adverse outcomes in patients with CKD and anaemia. We searched MEDLINE, EMBASE, and the Cochrane Library from 2002 until 2018 for studies reporting the incidence or prevalence of anaemia and associated risk factors and/or associations between haemoglobin (Hb) or anaemia and mortality, major adverse cardiac events (MACE), hospitalisation, or CKD progression in adult patients with CKD. Extracted data were summarised as risk factors related to the incidence or prevalence of anaemia or the risk (hazard ratio (HR)) of outcome by Hb level (<10, 10–12, >12 g/dL) in patients not on dialysis and in those receiving dialysis. 191 studies met the predefined inclusion criteria. The risk factor most associated with the prevalence of anaemia was CKD stage, followed by age and sex. Mean HRs (95% CI) for all-cause mortality in patients with CKD on dialysis with Hb <10, 10–12, and >12 g/dL were 1.56 (1.43–1.71), 1.17 (1.09–1.26), and 0.91 (0.87–0.96), respectively. Similar patterns were observed for nondialysis patients and for the risks of hospitalisation, MACE, and CKD progression. This is the first known systematic review to quantify the risk of adverse clinical outcomes based on Hb level in patients with CKD. Anaemia was consistently associated with greater mortality, hospitalisation, MACE, and CKD progression in patients with CKD, and risk increased with anaemia severity. Effective treatments that not only treat the anaemia but also reduce the risk of adverse clinical outcomes are essential to help reduce the burden of anaemia and its management in CKD.

1. Introduction

The worldwide prevalence of chronic kidney disease (CKD) is estimated to be 8–16% [1] and continues to grow, driven by ageing populations and increasing rates of obesity and type 2 diabetes mellitus. Type 2 diabetes and hypertension are the leading causes of CKD in the developed world [1], and the presence of CKD increases an individual’s risk of developing cardiovascular (CV) disease, hyperlipidaemia, mineral and bone disorders, and anaemia [2]. Anaemia—defined by the World Health Organization (WHO) as a blood Hb concentration of <12 g/dL for nonpregnant adult women and <13 g/dL for adult men [3]—is characterised by insufficient red blood cells and therefore haemoglobin (Hb), and common signs/symptoms include a pale appearance, fatigue, and dyspnoea (breathlessness).

The development of anaemia in patients with CKD is driven by at least two factors. First, compared with patients without CKD, those with CKD produce less erythropoietin (EPO), a hormone produced by the kidneys that stimulates red blood cell production [4], and second, hepcidin—a hormone that (at high levels) impairs dietary iron
2.1. Literature Search and Data Extraction. A SLR was conducted according to the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) checklist [7]. Searches were conducted to include studies published between 01 January 2002 and 31 August 2018 across the following electronic databases: PubMed (MEDLINE and MEDLINE In-Process), EMBASE, and the Cochrane Library. The electronic search strategies for each of the databases are included in the Supplementary Material (available here). In addition to the searching of databases and conference proceedings, a free text Internet search was conducted and reference lists from relevant studies were used to identify further studies that may meet eligibility criteria. Search strategies for each database are detailed in Supplementary Tables S1–S3.

Bibliographic details and abstracts of all citations retrieved by the literature search were downloaded into Endnote version X7. Titles and abstracts were independently assessed for eligibility by two reviewers. Full texts of potentially eligible studies were retrieved and assessed against the Population-Intervention-Comparators-Outcomes-Study (PICOS) eligibility criteria (Table 1) independently by two reviewers. Any discrepancies between the two reviewers concerning eligibility were resolved by consensus.

The inclusion criteria captured studies describing the incidence or prevalence of anaemia alongside associated risk factors and/or associations between Hb or anaemia and mortality, MACE, hospitalisation, or CKD progression in adult patients with CKD on dialysis or adult patients with CKD not on dialysis. “Associations” included all studies that reported relative or absolute measures of risk for mortality, hospitalisation, MACE, and CKD progression dependent on a patient’s Hb level or the presence of anaemia and were reported in terms of event incidence rate, probability of event, hazard ratio (HR), odds ratio (OR), relative risk ratio (RR), and incidence rate ratios (IRRs), irrespective of significance. Most studies reported measures of risk adjusted for baseline demographics and comorbidities, and the most adjusted measure was extracted for analysis. MACE included cardiovascular events, stroke, coronary heart (or artery) disease, heart failure, myocardial infarction, and atrial fibrillation. Studies conducted in paediatric patients or those reported in languages other than English were excluded. Data from studies that met the inclusion criteria were extracted by a single reviewer and quality-checked by a second reviewer. Due to wide heterogeneity in study design across the included studies, a quality assessment was not performed.

2.2. Analysis. Extracted data were tabulated to identify frequently reported risk factors associated with the development of anaemia in patients with CKD. Risk factors were grouped into broader categories for reporting, and those identified by more than one study were displayed graphically; however, due to heterogeneity of risk factor definitions within these categories, no formal quantitative analysis is presented regarding the relative magnitude of the effects of these risk factors on the incidence of adverse clinical outcomes.

A random-effects meta-analysis of the effects of Hb concentration on the risks of all-cause mortality, CV specific mortality, MACE, hospitalisation, and CKD progression (defined as progressing to end-stage renal disease (ESRD) or the initiation of renal replacement therapy (RRT)) was conducted for studies reporting outcomes of interest in patients with CKD not on dialysis and patients with CKD receiving dialysis. Note that CKD progression was only assessed in patients with CKD not on dialysis. The meta-analysis was conducted using R 3.4.0 [8] and the package meta [9] to account for study sample sizes and reported estimates of uncertainty.

To enable more consistent analysis of reported associations between Hb concentration and patient adverse outcomes (i.e., mortality, MACE, hospitalisation, and CKD progression), Hb concentration categories were converted to a single Hb value for analysis using the midpoint of the categorical range. Hb was grouped into the following categories for analysis: <10 g/dL, 10–12 g/dL, and >12 g/dL, and risk of each outcome attributed to each Hb grouping where data were available. If a study reported Hb without a defined lower limit (e.g., <9 g/dL), the upper defined limit minus 1 g/dL (i.e., 8 g/dL) was applied to that category prior to inclusion into the overall analysis. Similarly, if a study reported Hb without a defined upper limit (e.g., >13 g/dL), the lower defined limit plus 1 g/dL (i.e., 14 g/dL) was applied to that category prior to inclusion into the overall analysis. Where definitions of anaemia were not provided, a threshold value of 10 g/dL was assumed for anaemic patients and a threshold value of 13 g/dL was assumed for nonanaemic patients. Reference categories for relative measures of risk are as reported in their respective publications, and point estimates presented are based on the aggregation of relative measures of risk reported for each Hb category. Reported absolute measures of risk were converted to the corresponding relative measure for meta-analysis, using the highest Hb category as a reference.

The risk of each outcome was also expressed based on continuous Hb data (per 1 g/dL increase in Hb). Data reported are means (95% confidence interval (CI)). All reported estimates of associations between Hb or anaemia and...
patient outcomes were included in the analysis regardless of statistical significance.

3. Results

3.1. Summary of Included Studies. The searches identified 3734 references, after the removal of duplicates. After reviewing titles and abstracts, a further 2728 references were excluded. Full texts of the remaining 1006 references were retrieved and reviewed. Following full-text review, 191 references were deemed to satisfy the inclusion criteria and data were subsequently extracted for analysis (Figure 1). Of the 815 studies excluded following full-text review, 637 studies were excluded for not including variables (i.e., the use of haematocrit or red blood cell width distribution instead of Hb or the reporting of incidence or prevalence without associated risk factors) or outcomes (i.e., the risk of outcome was not reported in association with anaemia) of interest. Furthermore, 88 were conducted in non-CKD populations, 56 were excluded due to study design, and five were reported in languages other than English.

From the 191 included studies (Table 2), 75 were prospective, 65 were retrospective, 11 were observational, and 11 were randomised controlled trials; the design was unspecified in 29 studies. Total cohort sizes ranged from 50 to 1,136,201. Sixty-six of the included studies were conducted in Asia, 62 in North America, 48 in Europe, five in South America, four in Africa, two in Australia, and four were multinational. The majority of studies were conducted in either outpatient/renal clinic (n = 67) or hospital settings (n = 56), with small numbers undertaken in the community (n = 10); the setting was not reported in 58 studies.

3.2. Risk Factors Associated with Anaemia. The incidence or prevalence of anaemia was reported in 32 studies; prevalence was reported in n = 30, and incidence was reported in n = 2. 23 studies were conducted in CKD patient cohorts not on dialysis, one study in a dialysis cohort, and eight studies in cohorts that included both nondialysis and dialysis patients with CKD. There was significant heterogeneity in the definition of anaemia used across the included studies; however, there was no trend in the use of different Hb thresholds over time in line with changing recommendations. Whilst the most common definition of anaemia aligned with WHO guidelines for the diagnosis of anaemia [3], of Hb levels <13.0 g/dL in men and <12.0 g/dL in women (n = 13), thresholds ranged between 10.0 g/dL and 13.5 g/dL for men and 10.0 g/dL and 12.0 g/dL for women. Furthermore, not all studies reported separate thresholds for men and women. Risk factors associated with the presence of anaemia reported by more than one study are shown in Figure 2. The most frequently identified risk factor was eGFR or CKD stage (n = 30), followed by age (n = 10), sex (n = 10), race/ethnicity (n = 5), and albuminuria (n = 5). In all of these cases, patients with more severe renal impairment were at increased risk of experiencing anaemia.

3.3. Associations between Haemoglobin and Adverse Clinical Outcomes

3.3.1. Association between Haemoglobin and Mortality. An association between Hb concentration (or anaemia) and mortality was reported by 124 studies, with 42 studies conducted in CKD patient cohorts not on dialysis, 76 studies in dialysis cohorts, and six studies in cohorts that included both nondialysis and dialysis patients with CKD. One
hundred and nineteen and 13 studies identified similar relationships between Hb or anaemia and both all-cause mortality and CV mortality, respectively. Pooled mean HRs quantifying the risk of both all-cause and CV mortality based on Hb concentration are shown in Figure 3.

Pooled mean (95% CI) HRs for the risk of all-cause mortality in patients with CKD not on dialysis with Hb <10 g/dL (n=17) and 10–12 g/dL (n=1) were 1.70 (1.42–2.01) and 0.97 (0.92–1.01), respectively. No studies reported the risk of all-cause mortality in patients with CKD not on dialysis with Hb >12 g/dL. The HR of CV mortality in patients with CKD not on dialysis with Hb <10 g/dL was only reported by one study, with a median HR of 3.72 and wide CIs of 1.72 to 8.05.

The estimated HRs of all-cause mortality in patients with CKD on dialysis with Hb <10 g/dL (n=11), 10–12 g/dL (n=15), and >12 g/dL (n=8) were 1.56 (1.43–1.71), 1.17 (1.09–1.26), and 0.91 (0.87–0.96), respectively. The HRs of CV mortality in dialysis patients followed a similar pattern with HRs of 1.50 (1.32–1.70), 1.24 (1.09–1.40), and 1.00 (0.95–1.06) across Hb <10 g/dL (n=4), 10–12 g/dL (n=7), and >12 g/dL (n=4), respectively.

The HR of all-cause mortality and CV mortality when Hb concentration was reported as a continuous variable followed similar patterns to the categorical data, of decreasing risk with increasing Hb. Mean (95% CI) HRs for the overall risk of all-cause mortality in patients with CKD not on dialysis (n=18) and on dialysis (n=33) were 0.93 (0.91–0.95) and 0.86 (0.83–0.89) per 1 g/dL increase in Hb, respectively. The HR of CV mortality per 1 g/dL increase in Hb was 0.70 (0.52–0.94) and 0.87 (0.81–0.94) in patients with CKD not on dialysis (n=1) and on dialysis (n=1), respectively.

3.3.2. Association between Haemoglobin and Hospitalisation.

An association between Hb concentration (or anaemia) and hospitalisation was reported in 22 studies, with seven studies conducted in CKD patient cohorts not on dialysis, 14 studies in dialysis cohorts, and one study in a cohort that included both patients CKD not on dialysis and patients on dialysis. Mean HRs quantifying the risk of hospitalisation based on Hb concentration are shown in Figure 4 (left).

The pattern of association between Hb (or anaemia) and hospitalisation observed in the included studies tended to be similar to that observed between Hb and mortality, with lower Hb associated with higher risk of hospitalisation. The pooled mean (95% CI) HR for the risk hospitalisation in CKD patients not on dialysis with Hb <10 g/dL (n=2) was 1.46 (1.02–2.09). No studies reported the risk of hospitalisation in CKD patients not on dialysis with Hb of 10–12 g/dL or >12 g/dL. The HR of hospitalisation in patients on dialysis with Hb 10–12 g/dL (n=2) and >12 g/dL (n=2) were 1.09
| Author                  | Year | Country     | N     | NDD (%) | DD (%) | T2DM (%) | ESA use (%) | Incidence or prevalence of anaemia? | Association between anaemia and: |
|------------------------|------|-------------|-------|---------|--------|----------|-------------|---------------------------------|----------------------------------|
|                        |      |             |       |         |        |          |             |                                 | Mortality | Hospitalisation | MACE | CKD progression |
| Abramson et al. [10]   | 2003 | USA         | 13,716| 100.0   | 0.0    | 10.6     | NR          | NR                | N               | N               | Y    | N               |
| Ahmed et al. [11]      | 2010 | USA         | 79,985| 100.0   | 0.0    | 100.0    | NR          | 1.20              | Prevalence | N               | N    | N               |
| Ahn et al. [12]        | 2013 | Korea       | 984   | 100.0   | 0.0    | 24.0     | NR          | Prevalence | N               | N    | N               |
| Akizawa et al. [13]    | 2008 | Japan       | 5,788 | 100.0   | 0.0    | 28.6     | NR          | Prevalence | Y               | N    | N               |
| Akizawa et al. [14]    | 2014 | Japan       | 6631  | 0.0     | 100.0  | NR       | 100.0      | NR                | Y               | N    | N               |
| Akizawa et al. [15]    | 2016 | Japan       | NR    | 100.0   | 0.0    | 44.5     | 100.0      | NR                | Y               | Y    | Y               |
| Anees et al. [16]      | 2009 | Pakistan    | 185   | 0.0     | 100.0  | NR       | NR         | NR                | Y               | N    | N               |
| Anees et al. [17]      | 2010 | Pakistan    | 50    | 0.0     | 100.0  | NR       | 46.0       | NR                | N               | N    | N               |
| Antunes et al. [18]    | 2016 | Brazil      | 211   | 0.0     | 100.0  | 29.0     | NR         | NR                | N               | Y    | N               |
| Anutrakukhai et al. [19]| 2016 | Thailand    | 1,28,338 | 83.1 | 16.9 | 43.0 | NR | NR | Y | Y | N | N |
| Arun et al. [20]       | 2012 | India       | 100   | NR     | NR     | NR       | NR         | NR                | Prevalence | N               | N    | N               |
| Astor et al. [21]      | 2006 | USA         | 15,792| 100.0   | 0.0    | 11.6     | 0.0         | Prevalence | Y               | N    | Y               |
| Astor et al. [22]      | 2002 | USA         | 15,419| 100.0   | 0.0    | 5.0      | NR          | Prevalence | N               | N    | N               |
| Avram et al. [23]      | 2003 | USA         | 529   | 0.0     | 100.0  | 47.0     | NR          | NR                | Y               | N    | N               |
| Babua et al. [24]      | 2015 | Uganda      | 217   | 100.0   | 0.0    | 16.2     | NR          | Prevalence | N               | N    | N               |
| Bae et al. [25]        | 2015 | Korea       | 2,470 | 0.0     | 100.0  | 44.5     | NR          | NR                | Y               | N    | N               |
| Barrett Bowling et al. [26]| 2011 | USA         | 30,528| 100.0   | 0.0    | 7.74     | NR          | Prevalence | N               | N    | N               |
| Beck et al. [27]       | 2015 | Germany     | 5,015 | 100.0   | 0.0    | 35.2     | NR          | NR                | N               | N    | N               |
| Bello et al. [28]      | 2015 | USA         | 4,854 | 100.0   | 0.0    | 100.0    | 0.5         | NR                | N               | N    | N               |
| Bentata et al. [29]    | 2013 | Morocco     | 72    | 100.0   | 0.0    | 100.0    | NR          | NR                | N               | N    | N               |
| Bharti et al. [30]     | 2010 | USA         | 1358  | 0.0     | 100.0  | 51.8     | NR          | NR                | Y               | Y    | N               |
| Boudville et al. [31]  | 2009 | Multi continent | 6,165 | 100.0   | 0.0    | 36.2     | 49.0        | NR                | Y               | N    | N               |
| Bradbury et al. [32]   | 2009 | USA         | 6,133 | 0.0     | 100.0  | NR       | 100.0      | NR                | Y               | N    | N               |
| Bravo-Jaimes et al. [33]| 2015 | Peru        | 103   | 0.0     | 100.0  | NR       | NR         | NR                | N               | N    | Y               |
| Brunelli et al. [34]   | 2008 | USA         | 34,963| 0.0     | 100.0  | 45.0     | NR          | NR                | N               | N    | Y               |
| Brunelli et al. [35]   | 2008 | USA         | 6,644 | 0.0     | 100.0  | 24.8     | NR          | NR                | Y               | N    | N               |
| Buccianti et al. [36]  | 2004 | Italy       | 77    | 0.0     | 100.0  | 16.9     | NR          | NR                | Y               | N    | N               |
| Cana-Ruii et al. [37]  | 2013 | Romania     | 165   | 100.0   | 0.0    | 30.3     | NR          | NR                | N               | Y    | N               |
| Capelli et al. [38]    | 2008 | USA         | 687   | 0.0     | 100.0  | NR       | NR         | NR                | Y               | N    | N               |
| Chan et al. [39]       | 2009 | USA         | 1,00,835 | 0.0 | 100.0 | NR | NR | NR | N | Y | N |
| Chan et al. [40]       | 2017 | USA         | 87,302| 0.0     | 100.0  | 29.0     | NR          | NR                | N               | Y    | N               |
| Chang et al. [41]      | 2016 | Taiwan      | 1,530 | 100.0   | 0.0    | 38.5     | NR          | NR                | N               | N    | N               |
| Chen et al. [42]       | 2013 | China       | 6,325 | NR      | NR     | 100.0    | NR          | Prevalence | N               | N    | N               |
| Chen et al. [43]       | 2013 | Taiwan      | 439   | NR      | NR     | 57.4     | NR          | NR                | N               | N    | Y               |
| Chen et al. [44]       | 2012 | Taiwan      | 485   | 100.0   | 0.0    | 56.3     | NR          | NR                | N               | N    | N               |
| Chen et al. [45]       | 2016 | China       | 556   | 0.0     | 100.0  | 14.6     | 100.0       | NR                | Y               | N    | N               |
| Chen et al. [46]       | 2012 | China       | 822   | 100.0   | 0.0    | 20.2     | NR          | NR                | N               | N    | Y               |
| Chonchol et al. [47]   | 2008 | Italy       | 7,389 | 100.0   | 0.0    | NR       | NR          | Prevalence | N               | N    | N               |

Table 2: Characteristics of the included studies reporting the incidence or prevalence of anaemia and/or associations between anaemia and risk of mortality, hospitalisation, major adverse cardiac events, or CKD progression.
| Author                  | Year | Country   | N   | NDD (%) | DD (%) | T2DM (%) | ESA use (%) | Incidence or prevalence of anaemia? | Association between anaemia and: |
|------------------------|------|-----------|-----|---------|--------|----------|-------------|-------------------------------------|-------------------------------|
|                        |      |           |     |         |        |          |             |                                     | Mortality          | Hospitalisation | MACE | CKD progression |
| Christensen et al. [48]| 2002 | USA       | 174 | 100.0  | 0.0    | NR       | NR          | N                     | N                  | N               | N    | N               |
| Conway et al. [49]     | 2008 | USA       | 174 | 100.0  | 0.0    | 100.0    | NR          | N                     | Y                  | N               | Y    | Y               |
| De Nicola et al. [50]  | 2011 | Italy     | 1,248| 100.0  | 0.0    | 28.0     | 12.4        | N                     | Prevalence         | Y               | N    | N               |
| De Nicola et al. [51]  | 2012 | Italy     | 1,248| 100.0  | 0.0    | 27.7     | 12.4        | N                     | N                  | N               | N    | N               |
| De Nicola et al. [52]  | 2010 | Italy     | 668 | 100.0  | 0.0    | 22.6     | NR          | N                     | Y                  | N               | N    | N               |
| De Nicola et al. [53]  | 2017 | Italy     | 2,340| 100.0  | 0.0    | 30.6     | NR          | N                     | Y                  | N               | N    | N               |
| Desai et al. [54]      | 2011 | USA       | 995 | 100.0  | 0.0    | 100.0    | NR          | N                     | N                  | N               | N    | N               |
| Djukanović et al. [55] | 2015 | Serbia    | 2,153| 0.0    | 100.0  | NR       | 65.1        | N                     | Y                  | N               | N    | N               |
| Dmitrieva et al. [56]  | 2013 | UK        | 51,372| 100.0 | 0.0    | 28.0     | 12.4        | N                     | Prevalence          | N               | N    | N               |
| Drawz et al. [57]      | 2012 | USA       | 13,874| 100.0 | 0.0    | 38.8     | 1.8         | Y                     | Prevalence          | N               | N    | N               |
| Du Cheyron et al. [58] | 2005 | France    | 206 | 0.0    | 100.0  | 45.0     | NR          | N                     | Y                  | N               | N    | N               |
| Faller et al. [59]     | 2013 | France    | 155 | 100.0  | 0.0    | NR       | NR          | Y                     | N                  | N               | Y    | N               |
| Fathelrahman et al. [60]| 2012| Sudan     | 500 | 0.0    | 100.0  | NR       | NR          | Y                     | Y                  | Y               | N    | N               |
| Feldman et al. [61]    | 2004 | USA       | 27,280| 0.0   | 100.0  | 44.7     | 93.3        | N                     | N                  | N               | N    | N               |
| Feldman et al. [62]    | 2002 | USA       | 10,169| 0.0   | 100.0  | 40.9     | 87.4        | N                     | N                  | Y               | N    | N               |
| Ferrari et al. [63]    | 2009 | Australia | 8,752| 100.0  | 0.0    | NR       | NR          | Prevalence            | N                  | N               | N    | N               |
| Fort et al. [64]       | 2010 | Spain     | 2,310| 100.0  | 0.0    | 40.5     | NR          | N                     | Y                  | Y               | Y    | N               |
| Frankenfeld et al. [65] | 2003| USA       | 7,723| 100.0  | 0.0    | 40.5     | NR          | Y                     | N                  | N               | Y    | N               |
| Fraser et al. [66]     | 2014 | UK        | 1,707| 100.0  | 0.0    | 87.6     | NR          | Y                     | Y                  | N               | N    | N               |
| Fukuma et al. [67]     | 2012 | Japan     | 95,460| 0.0   | 100.0  | 32.5     | 100.0       | N                     | N                  | Y               | N    | N               |
| Garlo et al. [68]      | 2015 | USA       | 1,141| 100.0  | 0.0    | 62.8     | NR          | N                     | N                  | N               | Y    | N               |
| Go et al. [69]         | 2018 | USA       | 36,195| 100.0 | 0.0    | 36.0     | 0.7         | Y                     | N                  | N               | N    | N               |
| Goicoechea et al. [70] | 2004 | Spain     | 176 | 100.0  | 0.0    | 33.0     | NR          | N                     | N                  | N               | N    | Y               |
| Guan et al. [71]       | 2015 | China     | 102 | 100.0  | 0.0    | 100.0    | NR          | N                     | Y                  | N               | N    | N               |
| Han et al. [72]        | 2016 | Korea     | 17,373| 100.0| 0.0    | 9.4      | NR          | Prevalence            | N                  | N               | N    | N               |
| Hanafusa et al. [73]   | 2014 | Japan     | 3,341| 0.0    | 100.0  | 39.4     | NR          | Y                     | N                  | N               | N    | N               |
| Hasagawa et al. [74]   | 2018 | Japan     | 2,034| 100.0  | 0.0    | 38.6     | NR          | Y                     | N                  | N               | N    | N               |
| Hayashi et al. [75]    | 2013 | Japan     | 404 | 0.0    | 100.0  | 41.8     | 58.7        | N                     | N                  | Y               | N    | N               |
| He et al. [76]         | 2017 | USA       | 3,557| 100.0  | 0.0    | 46.3     | NR          | Prevalence            | N                  | Y               | Y    | N               |
| Herzog et al. [77]     | 2004 | USA       | 1,136,201| 100.0| 0.0| 16.5     | NR          | N                     | Y                  | N               | N    | N               |
| Hosseini et al. [78]   | 2014 | Iran      | 305 | 0.0    | 100.0  | 100.0    | NR          | Prevalence            | N                  | N               | N    | N               |
| Hung et al. [79]       | 2015 | Taiwan    | 326 | 100.0  | 0.0    | 45.4     | NR          | Y                     | N                  | N               | N    | Y               |
| Imori et al. [80]      | 2015 | Japan     | 951 | 100.0  | 0.0    | 37.6     | 11.8        | Y                     | Y                  | N               | N    | Y               |
| Imamović et al. [81]   | 2014 | Bosnia-Serbia-Slovenia | 442 | 0.0    | 100.0  | 32.0     | NR          | N                     | Y                  | N               | N    | N               |
| Inker et al. [82]      | 2011 | USA       | 30,528| 100.0| 0.0    | 6.50     | NR          | Prevalence            | N                  | N               | N    | N               |
| Inrig et al. [83]      | 2012 | USA       | 1,432| 100.0  | 0.0    | 31.2     | 100.0       | NR                    | N                  | N               | Y    | Y               |
| Isakov et al. [84]     | 2014 | Israel    | 18,474| NR   | NR     | NR       | Prevalence   | N                     | N                  | N               | N    | N               |
| Ishigami et al. [85]   | 2013 | Japan     | 349 | 0.0    | 100.0  | 37.5     | NR          | Y                     | N                  | N               | N    | N               |
| Ishigami et al. [86]   | 2018 | USA       | 5,801| 100.0  | 0.0    | 15.5     | NR          | Prevalence            | N                  | N               | Y    | N               |
| Author/Year | Country | N | NDD (%) | DD (%) | T2DM (%) | ESA use (%) | Incidence or prevalence of anaemia? | Association between anaemia and: |
|------------|---------|---|---------|--------|----------|-------------|-------------------------------------|---------------------------------|
| Ito et al. [87] | Japan | 127 | 0.0 | 100.0 | 16.0 | NR | NR | Mortality |
| Johnson et al. [88] | USA | 6,541 | 100.0 | 0.0 | 31.3 | NR | NR | Y |
| Johnson et al. [89] | USA | 7,982 | 100.0 | 0.0 | 28.0 | NR | NR | N |
| Joshi et al. [90] | China | 805 | 0.0 | 100.0 | NR | NR | NR | N |
| Joss et al. [91] | UK | 508 | NR | NR | 37.3 | NR | NR | N |
| Jung et al. [92] | Korea | NR | 100.0 | 0.0 | NR | NR | Y | N |
| Kataoka et al. [93] | Japan | 72 | 0.0 | 100.0 | NR | NR | NR | N |
| Keane et al. [94] | Multi continent | 1,513 | 100.0 | 0.0 | NR | NR | Y | N |
| Keane et al. [95] | Multi continent | 1,513 | 100.0 | 0.0 | NR | NR | Y | N |
| Keough-Ryan et al. [96] | Canada | 5,549 | 100.0 | 0.0 | 26.2 | NR | NR | N |
| Khan et al. [97] | Malaysia | 621 | 100.0 | 0.0 | 40.1 | NR | NR | N |
| Koveshy et al. [98] | USA | 861 | 100.0 | 0.0 | 53.1 | NR | NR | N |
| Koveshy et al. [99] | USA | 853 | 100.0 | 0.0 | 52.8 | NR | NR | N |
| Koveshy et al. [100] | USA | 860 | 100.0 | 0.0 | 52.8 | NR | NR | N |
| Kuo et al. [101] | Taiwan | 1,558 | 100.0 | 0.0 | 100.0 | NR | NR | Y |
| Kuo et al. [102] | Taiwan | 42,230 | 100.0 | 0.0 | 45.4 | NR | NR | Y |
| Kuwhara et al. [103] | Japan | 297 | 100.0 | 0.0 | NR | 100.0 | NR | N |
| Kwon et al. [104] | Korea | 1,276 | 100.0 | 0.0 | 52.4 | NR | NR | N |
| Lacson et al. [105] | USA | 78,420 | 100.0 | 0.0 | 51.9 | NR | NR | N |
| Lattanzio et al. [106] | Italy | 487 | NR | NR | 25.5 | NR | NR | N |
| Lau et al. [107] | Singapore | 457 | 100.0 | 0.0 | 64.6 | Incidence | N | N |
| Levin et al. [108] | Canada | 4,231 | 100.0 | 0.0 | 33.0 | NR | NR | Y |
| Levin et al. [109] | Canada | 3,028 | 100.0 | 0.0 | 28.0 | NR | NR | Y |
| Li Vecchi et al. [110] | Italy | 281 | NR | NR | 64.4 | NR | NR | N |
| Lin et al. [111] | Taiwan | 105 | 100.0 | 0.0 | NR | NR | Y | N |
| Lin et al. [112] | Taiwan | 445 | 100.0 | 0.0 | 44.5 | NR | NR | Y |
| Lin et al. [113] | Taiwan | NR | 100.0 | 0.0 | NR | NR | Y | N |
| Liu et al. [114] | China | 1,778 | 100.0 | 0.0 | 25.3 | NR | NR | Y |
| Locatelli et al. [115] | Europe | 4,591 | 100.0 | 0.0 | NR | NR | NR | Y |
| MacDougall et al. [116] | UK | 13,422 | 100.0 | 0.0 | NR | NR | Y | N |
| McCollan et al. [117] | USA | 5,222 | 100.0 | 0.0 | 64.4 | NR | NR | N |
| McCullough et al. [118] | USA | 37,153 | 100.0 | 0.0 | 26.2 | NR | NR | Y |
| McMahon et al. [119] | Australia | 302 | 100.0 | 0.0 | NR | 88.4 | NR | N |
| Messa et al. [120] | Italy | 568 | 100.0 | 0.0 | 28.9 | NR | NR | Y |
| Metcalfe et al. [121] | UK | 523 | 100.0 | 0.0 | 23.7 | NR | NR | Y |
| Minuto et al. [122] | Italy | 137 | 100.0 | 0.0 | 32.9 | 100.0 | NR | Y |
| Minuto et al. [123] | Italy | 194 | 100.0 | 0.0 | 34.0 | 100.0 | NR | Y |
| Minuto et al. [124] | Italy | 30,326 | 100.0 | 0.0 | 24.5 | NR | NR | Y |
| Mohanram et al. [125] | USA | 1,468 | 100.0 | 0.0 | NR | NR | N | Y |
| Mokoli et al. [126] | Kenya | 250 | 100.0 | 0.0 | NR | 51.6 | NR | N |
| Molnar et al. [127] | USA | 9,269 | 100.0 | 0.0 | 46.0 | NR | NR | N |
| Author                        | Year | Country | N     | Incidence or prevalence of anaemia? | Association between anaemia and: |
|------------------------------|------|---------|-------|-------------------------------------|----------------------------------|
| Moon et al. [128]            | 2011 | Korea   | 250   | Y                                   | Y                                |
| Nakazato et al. [129]        | 2015 | Japan   | 606   | Y                                   | Y                                |
| Neves et al. [130]           | 2016 | Portugal| 41,550| Y                                   | Y                                |
| Nishio et al. [131]          | 2013 | USA     | 417   | Y                                   | Y                                |
| Nakazato et al. [132]        | 2016 | Japan   | 606   | Y                                   | Y                                |
| Neves et al. [133]           | 2007 | Portugal| 299   | Y                                   | Y                                |
| Nishio et al. [134]          | 2013 | USA     | 1,677 | Y                                   | Y                                |
| Nakazato et al. [135]        | 2014 | Japan   | 9,058 | Y                                   | Y                                |
| Neves et al. [136]           | 2007 | Portugal| 9,058 | Y                                   | Y                                |
| Nishio et al. [137]          | 2013 | USA     | 1,677 | Y                                   | Y                                |
| Nakazato et al. [138]        | 2014 | Japan   | 9,058 | Y                                   | Y                                |
| Neves et al. [139]           | 2007 | Portugal| 9,058 | Y                                   | Y                                |
| Nishio et al. [140]          | 2013 | USA     | 1,677 | Y                                   | Y                                |
| Nakazato et al. [141]        | 2014 | Japan   | 9,058 | Y                                   | Y                                |
| Neves et al. [142]           | 2007 | Portugal| 9,058 | Y                                   | Y                                |
| Nishio et al. [143]          | 2013 | USA     | 1,677 | Y                                   | Y                                |
| Nakazato et al. [144]        | 2014 | Japan   | 9,058 | Y                                   | Y                                |
| Neves et al. [145]           | 2007 | Portugal| 9,058 | Y                                   | Y                                |
| Nishio et al. [146]          | 2013 | USA     | 1,677 | Y                                   | Y                                |
| Nakazato et al. [147]        | 2014 | Japan   | 9,058 | Y                                   | Y                                |
| Neves et al. [148]           | 2007 | Portugal| 9,058 | Y                                   | Y                                |
| Nishio et al. [149]          | 2013 | USA     | 1,677 | Y                                   | Y                                |
| Nakazato et al. [150]        | 2014 | Japan   | 9,058 | Y                                   | Y                                |
| Neves et al. [151]           | 2007 | Portugal| 9,058 | Y                                   | Y                                |
| Nishio et al. [152]          | 2013 | USA     | 1,677 | Y                                   | Y                                |
| Nakazato et al. [153]        | 2014 | Japan   | 9,058 | Y                                   | Y                                |
| Neves et al. [154]           | 2007 | Portugal| 9,058 | Y                                   | Y                                |
| Nishio et al. [155]          | 2013 | USA     | 1,677 | Y                                   | Y                                |
| Nakazato et al. [156]        | 2014 | Japan   | 9,058 | Y                                   | Y                                |
| Neves et al. [157]           | 2007 | Portugal| 9,058 | Y                                   | Y                                |
| Nishio et al. [158]          | 2013 | USA     | 1,677 | Y                                   | Y                                |
| Nakazato et al. [159]        | 2014 | Japan   | 9,058 | Y                                   | Y                                |
| Neves et al. [160]           | 2007 | Portugal| 9,058 | Y                                   | Y                                |
| Nishio et al. [161]          | 2013 | USA     | 1,677 | Y                                   | Y                                |
| Nakazato et al. [162]        | 2014 | Japan   | 9,058 | Y                                   | Y                                |
| Neves et al. [163]           | 2007 | Portugal| 9,058 | Y                                   | Y                                |
| Author                        | Year | Country         | N    | NDD (%) | DD (%) | T2DM (%) | ESA use (%) | Incidence or prevalence of anaemia? | Association between anaemia and: | Mortality | Hospitalisation | MACE | CKD progression |
|-------------------------------|------|-----------------|------|---------|--------|----------|-------------|-------------------------------------|----------------------------------|-----------|-----------------|------|-----------------|
| Teixeira et al. [169]         | 2015 | Brazil          | 162  | 0.0     | 100.0  | NR       | NR         | Y                                   | N                                | N         | N               | N    | N               |
| Thijssen et al. [170]         | 2012 | USA             | 6,838| 0.0     | 100.0  | 54.2     | NR         | Y                                   | N                                | N         | N               | N    | N               |
| Thorp et al. [171]            | 2009 | USA             | 5,885| 100.0   | 0.0    | 52.3     | 0.0        | N                                   | Y                                | Y         | Y               | N    | Y               |
| Toida et al. [172]            | 2017 | Japan           | 1,375| 100.0   | 0.0    | 32.4     | 0.0        | N                                   | Y                                | N         | N               | N    | N               |
| Tripepi et al. [173]          | 2010 | Italy           | 283  | 0.0     | 100.0  | 15.0     | 52.7       | N                                   | Y                                | N         | Y               | N    | N               |
| Tsubakihara et al. [174]      | 2015 | Japan           | 321  | 100.0   | 0.0    | 35.3     | NR         | Y                                   | N                                | N         | N               | N    | N               |
| Tsubakihara et al. [175]      | 2012 | Japan           | 322  | 100.0   | 0.0    | NR       | NR         | Y                                   | N                                | N         | N               | N    | N               |
| Ueda et al. [176]             | 2003 | Japan           | 202  | 100.0   | 0.0    | 100.0    | NR         | NR                                  | N                                | N         | N               | N    | N               |
| Vaičiúnienė et al. [177]      | 2010 | Lithuania       | 559  | 0.0     | 100.0  | NR       | NR         | Y                                   | N                                | N         | Y               | N    | N               |
| Van Diepen et al. [178]       | 2014 | Netherlands     | 394  | 0.0     | 100.0  | 100.0    | NR         | Y                                   | N                                | N         | N               | N    | N               |
| Varas et al. [179]            | 2018 | Spain           | 1,679| 0.0     | 100.0  | NR       | NR         | Y                                   | N                                | N         | N               | N    | N               |
| Vazquez et al. [180]          | 2009 | Spain           | 256  | 0.0     | 100.0  | 28.5     | NR         | N                                   | Y                                | N         | N               | N    | N               |
| Vejakama et al. [181]         | 2013 | Thailand        | 1,177| 0.0     | 100.0  | 21.2     | NR         | Y                                   | N                                | N         | N               | N    | N               |
| Vooymolen et al. [182]        | 2010 | Netherlands     | 547  | 100.0   | 0.0    | 23.6     | 25.1       | NR                                  | N                                | Y         | N               | N    | N               |
| Wagner et al. [183]           | 2011 | Germany         | 215  | 100.0   | 0.0    | 100.0    | 0.0        | N                                   | Y                                | N         | N               | N    | N               |
| Wagner et al. [184]           | 2011 | UK              | 5,447| 0.0     | 100.0  | 28.6     | NR         | NR                                  | N                                | N         | N               | N    | N               |
| Walker et al. [185]           | 2006 | USA             | 88,657| 100.0 | 0.0    | 19.6     | NR         | NR                                  | N                                | N         | N               | N    | N               |
| Weiner et al. [186]           | 2008 | USA             | 1,678| 100.0   | 0.0    | 15.0     | NR         | NR                                  | N                                | N         | N               | N    | N               |
| Weiner et al. [187]           | 2005 | USA             | 2,333| 100.0   | 0.0    | 17.1     | NR         | NR                                  | N                                | N         | N               | N    | N               |
| Weinhandl et al. [188]        | 2011 | USA             | 133,246| 0.0     | 100.0  | NR       | NR         | Y                                   | N                                | N         | N               | N    | N               |
| Wu et al. [189]               | 2013 | Taiwan          | 1,157| 100.0   | 0.0    | 0.48     | NR         | NR                                  | N                                | N         | N               | N    | N               |
| Xu et al. [190]               | 2012 | China           | 313  | 0.0     | 100.0  | 39.9     | NR         | NR                                  | Y                                | N         | N               | N    | N               |
| Yamamoto et al. [191]         | 2016 | Japan           | 2,602| 100.0   | 0.0    | 27.9     | 6.8        | NR                                  | Y                                | N         | N               | N    | N               |
| Yang et al. [192]             | 2007 | China           | 7,067| NR      | NR     | 100.0    | NR         | N                                   | N                                | N         | N               | Y    | N               |
| Yang et al. [193]             | 2007 | USA             | 34,963| 0.0     | 100.0  | 45.0     | NR         | N                                   | Y                                | N         | N               | N    | N               |
| Yang et al. [194]             | 2013 | China           | 809  | 0.0     | 100.0  | 23.4     | NR         | N                                   | Y                                | N         | N               | N    | N               |
| Yeates et al. [195]           | 2007 | Canada          | 26,316| 0.0     | 100.0  | NR       | NR         | Y                                   | N                                | N         | N               | N    | N               |
| Yotsuenda et al. [196]        | 2018 | Japan           | 3,436| 0.0     | 100.0  | 28.9     | 100.0      | NR                                  | N                                | N         | N               | N    | N               |
| Zhang et al. [197]            | 2015 | China           | 421  | 0.0     | 100.0  | 28.7     | NR         | NR                                  | Y                                | N         | N               | N    | N               |
| Ziginskiene et al. [198]      | 2013 | Lithuania       | 559  | 0.0     | 100.0  | NR       | NR         | Y                                   | N                                | N         | N               | N    | N               |
| Zitt et al. [199]             | 2014 | Austria         | 235  | 0.0     | 100.0  | 34.9     | 77.9       | NR                                  | N                                | Y         | N               | N    | N               |
| Zoppini et al. [200]          | 2010 | Italy           | 1,153| 100.0   | 0.0    | 100.0    | NR         | NR                                  | Y                                | N         | N               | N    | N               |

CKD: chronic kidney disease; DD: dialysis dependent; ESA: erythropoietin-stimulating agent; MACE: major adverse cardiac events; N; no; NDD: nondialysis dependent; NR: not reported; T2DM: type 2 diabetes mellitus; Y: yes.
No studies reported the risk of all-cause mortality in CKD patients not on dialysis with Hb of 10–12 g/dL or >12 g/dL. The overall risk of hospitalisation when Hb concentration was reported as a continuous variable followed a similar pattern to the categorical data, of decreasing risk with increasing Hb. The mean (95% CI) HR for the risk of hospitalisation in dialysis patients (n = 4) was 0.92 (0.87–0.98) per 1 g/dL increase in Hb. No studies reported the risk of hospitalisation in CKD patients not on dialysis where Hb was expressed as a continuous variable.

### 3.3.3. Association between Haemoglobin and Major Adverse Cardiac Events

An association between Hb concentration (or anaemia) and MACE was reported by 30 studies. Whilst some studies reported MACE specifically, others reported single components of MACE such as stroke, heart failure, and myocardial infarction; all MACE-type events were grouped for combined analysis in this SLR. 19 were studies conducted in CKD patient cohorts not on dialysis, seven studies in dialysis cohorts, and four studies that included both CKD patients not on dialysis and patients on dialysis. Mean HRs quantifying the risk of MACE based on Hb

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![Risk factors associated with the presence of anaemia identified by more than one included study.](image1)

**Figure 2:** Risk factors associated with the presence of anaemia identified by more than one included study.

![Associations between Hb level and mortality in CKD patients.](image2)

**Figure 3:** Associations between Hb level and mortality in CKD patients.
concentration are shown in Figure 4 (middle). The risks of MACE with anaemia tended to follow a similar pattern to the risks of mortality and hospitalisations, with higher levels of risk associated with lower Hb levels.

The mean (95% CI) HR for the risk MACE in CKD patients not on dialysis with Hb < 10 g/dL (n = 6) was 1.44 (1.17–1.76). The estimated HRs of MACE in patients on dialysis with Hb < 10 g/dL (n = 1), 10–12 g/dL (n = 2), and >12 g/dL (n = 1) were 2.31 (1.14–4.66), 1.19 (0.96–1.46), and 0.88 (0.74–1.04), respectively.

The overall risk of MACE in CKD patients when Hb concentration was expressed as a continuous variable followed a similar pattern to the categorical data, of decreasing risk with increasing Hb. The mean (95% CI) HRs for MACE in CKD patients not on dialysis (n = 5) and on dialysis (n = 2) were 0.92 (0.86–0.99) and 0.72 (0.21–2.46) per 1 g/dL increase in Hb, respectively.

4. Discussion

The aim of this review was to identify in a systematic manner the studies that reported risk factors associated with the presence of anaemia in patients with CKD and studies that characterised the association between anaemia (Hb level) and outcomes in patients with CKD. In doing so, we have summarised a contemporary evidence base of the risks of anaemia in CKD patients. In total, 191 studies that reported risk factors associated with anaemia in CKD and/or associations between Hb and mortality, hospitalisation, MACE, and CKD progression were identified. Overall, more severe anaemia was consistently associated with a greater risk of adverse outcomes.

The incidence or prevalence of anaemia in patients with CKD was reported in 31 studies identified by this systematic review. Anaemia is relatively common in CKD patients especially with increasing disease severity, with rates of up to 90% in Stage 5 patients. Studies from the UK [201] and USA [202] reported overall prevalence rates of anaemia in CKD patients with diabetes of 22% and 15%, ranging from 5% and 8% in Stage 1 up to 46% and 53% in Stage 5, respectively. Higher overall prevalence rates (32% and 52%) have been reported in studies of Malaysian [203] and Chinese [204] patients, with prevalence ranging from 13% and 22% in Stage 1 up to 70% and 90% in Stage 5, respectively.

The most commonly reported risk factor for the development of anaemia was eGFR (or CKD stage). Data consistently indicated that more severe CKD was associated with greater prevalence of anaemia. There are a number of pathophysiological mechanisms responsible for the development of anaemia alongside CKD. Compared to patients with anaemia without CKD, diseased kidneys produce less EPO than would normally be expected relative to the degree of anaemia. Whether this insufficient EPO is due to an absolute reduction in production capacity or an impaired sensitivity of kidney cells to the low tissue oxygenation that would normally stimulate production is unknown [205, 206]. More recent research has identified hepcidin as a
key hormone implicated in disordered iron homeostasis in CKD patients. When elevated, hepcidin impairs dietary iron absorption and reduces the mobilisation of stored iron, further contributing to anaemia [207, 208]. Overall, anaemia in CKD is likely to be multifactorial and other factors such as shortened red blood cell survival, greater blood losses (especially in dialysis patients), and impaired absorption of dietary iron may further exacerbate the condition [4].

Older age and female sex were also commonly identified as a risk factors involved in the development of anaemia in patients with CKD. Older age is associated with greater inflammation and age-related comorbidities. The presence of proinflammatory cytokines (e.g., IL-6) increases hepcidin expression [209], likely placing older patients at higher risk of developing anaemia. Furthermore, sex hormone regulation is also impacted with older age, and both testosterone and oestrogen have been shown to reduce circulating hepcidin [210, 211]. Despite lower Hb thresholds for anaemia diagnosis in females (<12 g/dL vs. <13 g/dL for males), female patients with CKD tended to be at higher risk of developing anaemia than their male counterparts. Indeed, McClellan et al. [117] found that female patients with CKD were approximately two times more likely to develop anaemia than males. Race or ethnicity has also been identified as factors that affect the prevalence of anaemia in patients with CKD [212].

The majority of risk factors reported in the included studies were patient characteristics or comorbidities. Despite EPO and hepcidin playing a significant role in the development of anaemia in patients with CKD, only two studies identified in this SLR assessed the role of EPO as a risk factor for anaemia and no studies included hepcidin. Further work on these laboratory-based variables and their role in the risk of anaemia associated with varying levels of each biochemical parameter would be helpful to better understand the development of anaemia in patients with CKD.

Anaemia was associated with higher risks of all-cause mortality, CV mortality, MACE, hospitalisations, and CKD progression. The effects tended to increase with anaemia severity, such that a Hb < 10 g/dL was linked to comparable or higher risk of each outcome than a Hb of 10–12 g/dL. Although the effects tended to be consistent across CKD patients not on dialysis and those patients on dialysis in terms of direction, the magnitude of the risks of all-cause and CV mortality in patients with CKD not receiving dialysis appears to be greater than for those not on dialysis. The reason for this is unclear; however, due to small study numbers in some groups and an inability to control for other variables in the study populations, this finding should be interpreted with caution and may warrant further investigation. Nevertheless, the reasons for the association between anaemia and poorer outcomes are not well understood. Chronic anaemia is associated with increased cardiac output and reduced systemic vascular resistance. The low blood pressure resulting from systemic vasodilatation may initiate a cascade of events, including increased sympathetic nervous activity and activation of the renin-angiotensin-aldosterone system to reduce salt and water excretion, thereby resulting in plasma volume expansion and oedema [213]. Overall, these changes result in greater cardiovascular workload, increasing the risk of conditions such as left ventricular hypertrophy [214, 215], and may contribute to the observation of higher rates of mortality, MACE, and hospitalisations observed with anaemia in CKD patients.

Anaemia is a common contributor to poor quality of life in patients with CKD but is also likely to be the factor that is most responsive to treatment [6]. Treatment of anaemia in CKD typically involves the use of supplemental iron (either oral or intravenous) and erythropoiesis-stimulating agents (ESAs) [205]. Supplemental iron may help improve iron status; however, it is not symptom- or risk-free and—depending on the mechanism(s) responsible for the anaemia—may not treat the condition adequately. ESAs mimic erythropoietin and act to stimulate red blood cell production in the bone marrow. However, although ESAs are successful at increasing haemoglobin levels in the majority of cases, they have not been shown to reduce the risks of adverse outcomes associated with anaemia in CKD patients [6] and may even result in increased risk of negative outcomes, as evidenced by three large randomised controlled trials [216–218].

The TREAT [218] study assessed the effect of darbepoetin alfa (ESA) versus placebo in more than 4000 patients with CKD, type 2 diabetes, and anaemia. HRs for death or CV event and for death or ESRD were similar; however, treatment group patients were almost two times more likely to suffer stroke (HR: 1.92 (95% CI: 1.38–2.65); p < 0.001) than control group patients. Additional studies have assessed the effect of ESA treatment based on different Hb target levels. The CREATE [217] trial assessed the effect of epoetin beta (ESA) administration on CV events in 603 patients with Stage 3 or 4 CKD and mild-to-moderate anaemia (Hb 11.0–12.5 g/dL). Patients were randomly assigned to receive ESA treatment to target a Hb level of 13.0–15.0 g/dL or to only receive the ESA if their Hb dropped below 10.5 g/dL (so as to maintain Hb 10.5–11.5 g/dL). ESA treatment successfully maintained Hb within predetermined ranges; however, treatment to normalise Hb (within 13.0–15.0 g/dL) was not associated with a reduction in the risk of CV events. Furthermore, the CHOIR [216] study involved the prescription of epoetin alfa (ESA) in 1400 patients with CKD to achieve a target Hb of either 13.5 g/dL (high) or 11.3 g/dL (low). Patients in the high Hb group experienced increased risk of composite (death, myocardial infarction, hospitalisation for congestive heart failure, or stroke) events (HR: 1.34 (95% CI: 1.03–1.74); p = 0.03) and no improvement in quality of life. Post hoc analyses from this study indicate that higher ESA doses (irrespective of Hb achieved) were the primary driver for the risk of adverse outcomes [219], indicating there is a need for more effective treatments.

Based on these trials, it is clear that high Hb targets should be avoided; however, it is unclear whether the poorer outcomes are due to the ESAs themselves or factors that often accompany low Hb such as inflammation, elevated hepcidin levels, blood loss, and/or malnutrition [4]. Ultimately, this uncertainty in trying to balance the risks of untreated anaemia against the risks of treatment with ESAs...
has led to frustration amongst many in the clinical community. With no clear effective intervention available to both restore Hb levels and improve outcomes, Hb remains little more than a biomarker for adverse outcomes in patients with CKD. This study is not without limitations. There was wide heterogeneity—as evidenced by I-squared statistic—in the study design, study size, patient characteristics, treatments received, outcomes (e.g., coding systems of hospitalisations), and anaemia definitions. Such variations in reporting of variables and outcomes meant that large numbers of studies were either excluded or were unable to be included in the final analysis that summarised HRs for the risk of each outcome. Furthermore, when outcome data were subdivided by Hb category and by patients receiving dialysis or not, many gaps were apparent, preventing full understanding of the level of risk. A SLR is also limited by the data available in each individual study. Whilst the most adjusted (for demographics and comorbidities) measure of risk was preferentially extracted, not all studies performed this level of analysis which may affect the overall estimate of risk.

As with all SLRs, there is also the potential for publication bias to impact on the generalisability of results. Furthermore, geographical bias may also affect the generalisability of the findings. The majority of included studies were conducted in Asia, North America, and Europe, with small study numbers in other regions. Despite this, the findings were relatively consistent irrespective of geographical location, indicating the findings are relatively generalisable across different countries and different ethnic backgrounds. The majority of studies included in this review also only presented relative risks of adverse outcomes associated with Hb or anaemia, and in general, there is a lack of information regarding the absolute risks of outcomes in these patients which may present an avenue for future research. However, the number of identified studies and the size of the cohorts represented in this review allow the formulation of an overarching summary of the associated risks to patients with anaemia.

5. Conclusion

This is the first known systematic review to quantify the risks of mortality, hospitalisation, MACE, and CKD progression associated with anaemia severity in patients with CKD. Anaemia was associated with greater risk of all clinical outcomes, and the risk increased with anaemia severity. The burden of CKD and its complications is substantial and projected to increase. Effective treatments that not only treat the anaemia but also reduce the risk of adverse clinical outcomes are essential to help reduce the burden of anaemia and its management in CKD.

Data Availability

The data supporting this systematic review are from previously reported studies and datasets, which have been cited. The processed data are available from the corresponding author on reasonable request.

Conflicts of Interest

EP, SG, and HvH are employees of AstraZeneca. PM and OD are employed by a company providing research and dissemination services to AstraZeneca and other pharmaceutical companies.

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Supplementary Materials

Table S1: MEDLINE search strategy. Table S2: EMBASE search strategy. Table S3: Cochrane Library search strategy. (Supplementary Materials)

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