Prognostic impact of comorbidity measures on outcomes following acute coronary syndrome: a systematic review

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Received: 23 February 2021 | Accepted: 7 May 2021

DOI: 10.1111/ijcp.14345

SYSTEMATIC REVIEW

Cardiovascular medicine

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE WILEY

Prognostic impact of comorbidity measures on outcomes following acute coronary syndrome: A systematic review

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Abstract

Aim: To identify existing comorbidity measures and summarise their association with acute coronary syndrome (ACS) outcomes.

Methods: We searched published studies from MEDLINE (OVIDSP) and EMBASE from inception to March 2021, studies of the pre-specified conference proceedings from Web of Science since May 2017, and studies included in any relevant systematic reviews. Studies that reported no comorbidity measures, no association of comorbid burden with ACS outcomes, or only used a comorbidity measure as a confounder without further information were excluded. After independent screening by three reviewers, data extraction and risk of bias assessment of each included study was undertaken. Results were narratively synthesised.

Results: Of 4166 potentially eligible studies identified, 12 (combined n = 6 885 982 participants) were included. Most studies had a high risk of bias at quality assessment. Six different types of comorbidity measures were identified with the Charlson comorbidity index (CCI) the most widely used measure among studies. Overall, the greater the comorbid burden or the higher comorbidity scores recorded, the greater was the association with the risk of mortality.

Conclusion: The review summarised different comorbidity measures and reported that higher comorbidity scores were associated with worse ACS outcomes. The CCI is the most widely measure of comorbid burden and shows additive value to clinical risk scores in use.

Review criteria

Observational studies reporting associations between comorbidity measures and ACS outcomes were identified using bibliographical searches of Medline, EMBASE and Web of Science. All articles were screened for eligibility using the pre-defined inclusion criteria. Meta-analysis was not possible due to differences in the study designs and outcomes in different studies.

Message for the clinic

CCI is the most widely used comorbidity measure to investigate the relationship between comorbid burden and outcomes in patients with ACS. While comorbidity burden according to all

six measures was associated with worse outcomes in the context of ACS, our review of model comparisons suggests that ECS might have better performance than CCI in predicting adverse outcomes.

1 | INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of death globally, representing 31% of all deaths.[1] Acute coronary syndromes (ACS) are a common acute presentation of CVD and are associated with significant morbidity, mortality and economic burden to society.[2] As the world's population is ageing rapidly, one consequence is the increase in the prevalence of chronic comorbid diseases, particularly in cardiovascular conditions such as in ACS. Comorbidity is the presence of more than one additional condition co-occurring with a primary condition.[3] It is well established that patients with a significant comorbidity burden are at increased risk of adverse outcomes and are challenging to treat.[4] Increasing comorbidity burden in patients with ACS is associated with an increased risk of mortality and future cardiovascular events.[5,6] Comorbidities rarely occur in isolation, with ACS patients often having multiple comorbidities[7] that increases the complexity of clinical decision-making in these patients.[8,9]

The Charlson comorbidity index (CCI) and the Elixhauser comorbidity score (ECS) are measures of global comorbid burden and have both been widely used to predict prognosis amongst different medical conditions.[10,11] The original CCI is a measure of co-morbidity burden and provides a means of quantifying the prognostic impact of 19 comorbid conditions on the basis of their number and individual impact by means of a score developed as a prognostic indicator for patients with a variety of medical conditions.[12-14] The ECS is another measure of comorbid burden and comprises 30 comorbidity measures used to derive a weighted comorbidity score (van Walraven ECS) to assess global comorbid burden.[15,16]

Previous systematic reviews assessing the prognostic impact of comorbid burden have been restricted to CCI and reported a positive association between higher CCI scores and risk of mortality in patients with ACS.[17] However, several other studies have evaluated the prognostic value of other comorbidity measures in ACS patients[18,19] with some literature indicating that ECS and other comorbidity measures might outperform CCI scores in outcome prediction.[20,21] There is still no systematic review conducted to summarise the totality of this evidence. Hence, the purpose of this systematic review is to identify existing comorbidity measures or indices that were used in ACS patients and report their associations with ACS outcomes.

2 | METHODS

We registered the protocol used for this review in the international prospective register of systematic reviews (PROSPERO registration number: CRD42019138044). The review was conducted according to the guidance of systematic review and meta-analysis for prognostic factor studies proposed by Riley et al.[22]

2.1 | Data sources and searches

The bibliographic databases (MEDLINE (OvidSP), EMBASE (OvidSP)) were searched to identify all potentially relevant published studies from inception to March 2021. Web of Science was searched to identify potentially relevant unpublished abstracts from the following three conference journals: American Heart Association (AHA), American College of Cardiology (ACC) and European Society of Cardiology (ESC) from 2017 onwards. Reference lists of all included studies were scrutinised, especially the primary studies included in the relevant systematic reviews identified from each database. Searches used broad terms and combinations of these terms that were related to the concept of three core terms: ACS, comorbidity and measure (Table S1). Search strategies combined a series of keywords with the most inclusive suffix and database-specific Medical Subject Heading terms (MeSH) with appropriate Boolean operators (Table S1). Our search strategies were further refined in consultation with an internal systematic review team prior to final execution.

2.2 | Study selection

2.2.1 | Inclusion criteria

The criteria for study selection mainly encompass the five domains: search designs, publication types, patient population, clinical outcomes and comorbidity measures. More detailed inclusion and exclusion criteria for the review are provided in Table S2.

Study design

Our literature search included randomized control trials (RCTs) as well as observational (cohort and case-control) studies. No language restriction was imposed. Non-human articles and study design papers were excluded.

Population of interest/outcome of interest

Selected studies were limited to patients hospitalised for an ACS. ACS was defined as either acute myocardial infarction (MI) (ST-elevated myocardial infarction (STEMI) and non-ST elevated myocardial infarction (NSTEMI)) or Unstable angina (UA). Studies with patients presenting without acute MI (such as stable angina, coronary heart disease, elective percutaneous coronary intervention

(PCI) and angiogram) were excluded. Outcomes of interest were one of the following three with no restriction on time point of outcome measurement: (1) mortality, (2) major adverse cardiac and cerebrovascular events (MACCE) and (3) bleeding.

Comorbidity measures as prognostic factors

Comorbid burden of patients was measured by composite comorbidity measures (scores or indexes). The comorbidity measures could be developed based on a simple count of comorbidities or on a numerical system with weightings assigned to individual comorbidities to produce a final weighted score. Studies must report at least one comorbidity measure (score or index) as primary prognostic factors used to predict the association of comorbid burden with ACS outcomes. It was agreed (decided by consensus of JE, GP and MAM) that studies only applying comorbidity measure as a confounder without estimate effects of outcomes were excluded.

2.2.2 | Selection process

We used references management software (Rayyan) to screen the studies and record reviewer decisions. After removing duplicates, every abstract was screened independently by two reviewers (FZ and CW) based on our inclusion and exclusion criteria defined above. Subsequently, any potentially relevant articles were obtained for full text review independently by three reviewers (FZ, CW and YC). The final study inclusion was decided by the senior authors (JE, GP and MAM).

2.3 | Data extraction and quality appraisal

Data extraction was completed independently by three reviewers using a pre-formatted Excel spreadsheet according to the critical appraisal and data extraction for systematic reviews of prognostic factor studies (CHARMS-PF) checklist.[22,23] We contacted the authors of included studies where necessary data was missing or methodological information was not clear. Information collected from the studies include the authors, year of publication, country, study design, study population, patient characteristics, sample size, database used, outcomes, design of comorbidity measures, variables included in comorbidity measures, modelling method and how comorbidity measures were included in the model (continuous or categorical), association between comorbid burden and outcomes, prognostic effect estimates and their confidence intervals (CIs), adjustment factors used, if validated or not, and summary of main findings.

Quality assessment of the studies was performed using the Quality In Prognostic factor Studies (QUIPS) checklist.[24,25] This tool was originally developed in 2006[25] and refined by Hayden and colleagues in 2013 for systematic reviews of prognostic factor studies by examining risk of bias (RoB) across the following six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, adjustment for other prognostic factors, and statistical analysis and reporting. Each of the six domains includes several prompting items, which were taken together to obtain the judgement of risk of bias in each domain (high, moderate, or low risk of bias). The method used to determine the overall risk of bias for each study was described by Grooten et al[25]: A study having six low RoB or only having one moderate RoB was classified as low RoB (green); if more than one domain were assessed as high RoB, or ≥3 moderate RoB, then this article was treated as high RoB (red); the remaining papers in between were considered as moderate RoB (yellow). Three reviewers independently completed this assessment, and the final decisions were reviewed and made by the senior authors.

2.4 | Data synthesis and analysis

A narrative synthesis was conducted instead of implementing a meta-analysis, due to the heterogeneity related to the length of follow-up, modelling used, how the comorbidity measure was modelled, adjustment variables used, and ACS presentation. Data were summarised across studies and interpreted by (1) describing the characteristics of the included studies, (2) determining the design of comorbidity measures used to define the comorbid burden and identifying how comorbidity measures were coded in the model and (3) synthesising the association between comorbid burden and ACS outcomes and the prognostic effect sizes.

3 | RESULTS

A total of 4166 studies were retrieved from our search. After excluding studies that did not meet the inclusion criteria, a total of four retrospective studies[26-29] and eight prospective studies[18,19,30-35] were included (Figure 1). In addition, we identified another 10 studies[20,21,36-43] that did not report any prognostic impact of comorbidity measure on ACS outcomes however offered information on model comparison in terms of predictive performance of different comorbidity measures.

3.1 | Characteristics of the included studies

The study designs and cohort characteristics of each included paper are presented in Table 1. Among four retrospective studies, one[26] had a follow up of 24 years, two had an 11-year follow-up,[27,28] one had a follow up of one year.[29] The remaining eight prospective studies had follow-up duration between half a year and ten years.[18,19,30-35] Eight studies were conducted between 1984 and 2008 and published between 2004 and 2019, four studies that were published in 2020 used relatively new data (year 2004-2016). The majority of the studies were conducted in European countries including five from Spain,[19,31,32,34,35] one from Italy,[30] one from Denmark[26] and one from Switzerland,[33] with the exception of one from Israel[18]

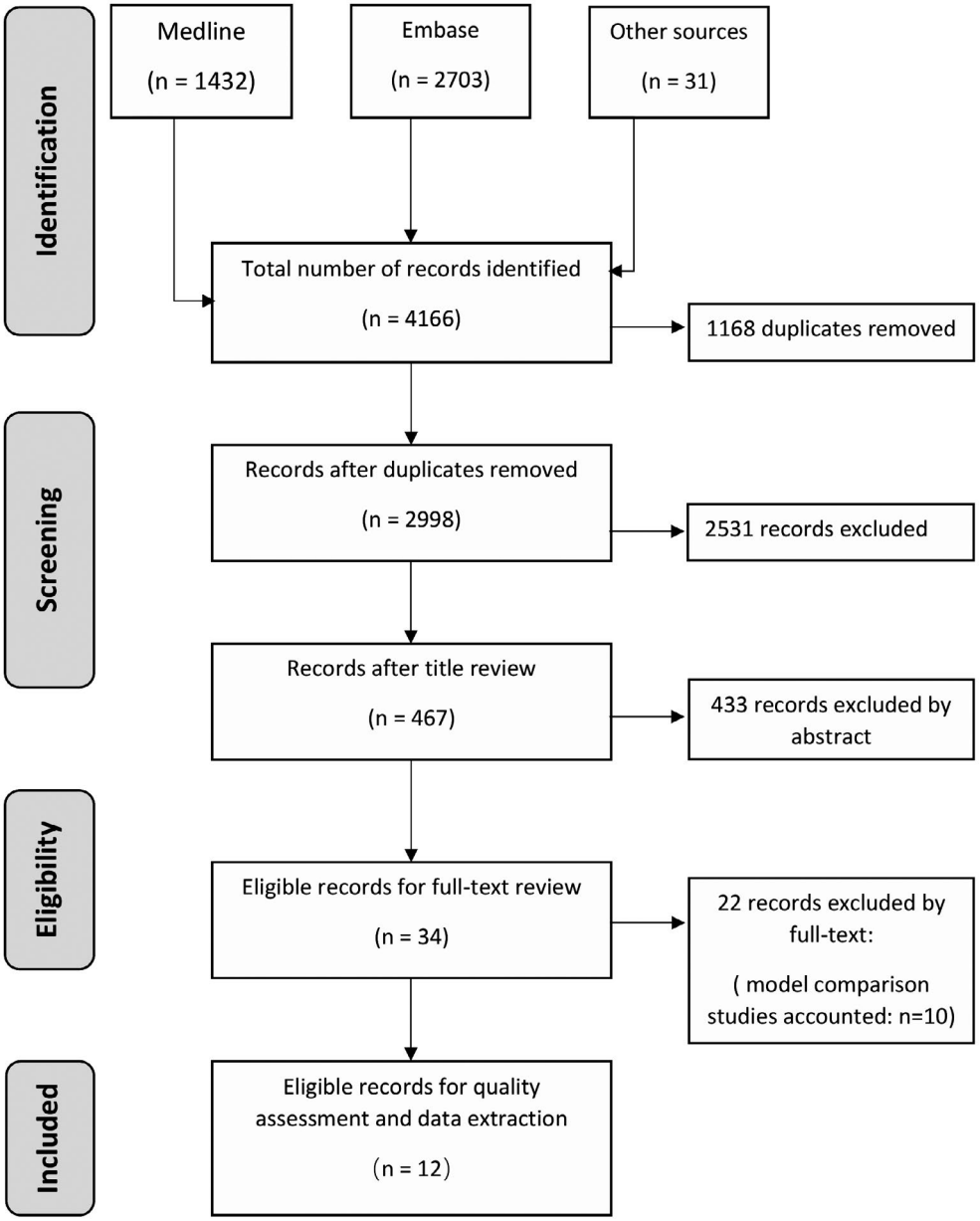


FIGURE 1 Screening flowchart of articles for the systemic review

and two from the United States.[27,28] Most studies were published as a full research manuscript although two were published as an abstract.[32,34] There was no age limitation in most studies except three studies[26-28] with an age limit of 15 years old or higher and two studies[19,34] which focused on patients aged ≥65 years and aged ≥80 years, respectively.

Our review included a total of 6 885 982 patients with the sample size of individual studies ranging from 520 to 6 613 623 patients. The study populations comprised patients with ACS (N = 6 645 339 in five study[27-29,33,34]), those with AMI (total N = 237 251 in three studies[18,26,31]), those with NSTEMI (total N = 2652 in three studies[19,32,35]), and those with STEMI (N = 740 in one study[30]). The mean ages ranged from 66 to 74 years old from studies which reported such data. The percentages of female patients varied between 27% and 42%.

3.2 | Quality assessment of the included studies

Risk of bias (RoB) assessment based on the QUIPS tool showed that seven studies[18,19,30-32,34,35] were at high RoB (see Figure 2) mainly due to lack of information on 'study attrition, prognostic factor measurement, statistical analysis and reporting' domains (eg, no information on response rate for study participants,[35] no description of patients who dropped out,[30] methodological issues,[32] or selective reporting of results).[30,34] Two studies from Radovanovic et al[33] and Hautamaki et al[29] were moderate RoB. Only three studies left[26-28] were evaluated as low RoB. Seven studies were at low RoB in the 'outcome measurement' domain, whilst more than two thirds of studies were at low RoB in 'study participation and study confounding' domains.

TABLE 1 Study design and characteristics of the included studies

Study ID	Study design; year; country	Study population size; type of population	Age (median, mean ± SD, %)	Female (%)	Description of inclusion for participants
Schmidt 2012	Retrospective cohort study; 1984-2008; Denmark	234 331 AMI	Women: median 74 in 1984 to median 77 in 2008; Men: median 68	37.9%	All first-time hospitalizations for MI among Danish-born inhabitants aged 15 years or older.
Plakht 2010	Prospective cohort study; 2002-2004; Israel	1885 AMI	<65, 44.6% 65-75, 26.3% >75, 29.1%	31.6%	No age limitation. Patients who had been admitted with AMI and discharged alive from hospital.
Sanchis 2019	Prospective cohort study; 2002-2008 and 2010-2012; Spain	920 NSTEACS	76.4 ± 7.0	42%	Elderly (≥65) patients admitted for NSTEACS.
Balzi 2005	Prospective cohort study; 2000-2001; Italy	740 STEMI	69.5 ± 12.2	30.1%	No age limitation. All residents in the Florence area arriving alive to the emergency department of one of the six hospitals with a suspected STEMI.
Sanchis 2011	Prospective cohort study; 2002-2008, Spain	1017 NSTEACS	68 ± 13	34%	No age limitation. The patients who admitted to the Hospital with NSTEACS.
Núñez 2004	Prospective cohort study; 2000-2003; Spain	1035 AMI (508 STEMI, 527 NSTEMI)	68 ± 3	32.1%	No age limitation. Patients diagnosed with AMI who were admitted to hospital.
Ramirez-Marrero 2011	Prospective cohort study; 2004-2005; Spain	715 NSTEACS	66.2 ± 11.2	NA	No age limitation. Patients admitted to hospital for NSTEACS.
Radovanovic 2014	Prospective cohort study; 2002-2012; Swiss	29 620 ACS	66.3 ± 12.8	27%	No age limitation All ACS patients. ACS included acute MI and unstable angina.
Zhang 2020	Retrospective cross-sectional study; 2004-2014; United State	6 613 623 ACS	67 (56-79)	40.0%	All adults (≥18 years) with the principal diagnosis of ACS.
Zhang 2020	Retrospective cross-sectional study; 2004-2014; US	6 613 623 ACS	67 (56-79)	40.0%	All adults (≥18 years) with the principal diagnosis of ACS.
Pastor 2019	Prospective cohort study; no study period found; Spain	520 ACS	84.4 ± 3.6	38.5%	Elderly (≥80 years) patients hospitalised after NSTEACS.
Hautamäki 2020	Retrospect cohort study; 2015-2016; Finland	1576 ACS	69.3 ± 11.8	30.9%	Patients who underwent invasive evaluation by coronary angiography for a first episode of suspected ACS during a two-year period.

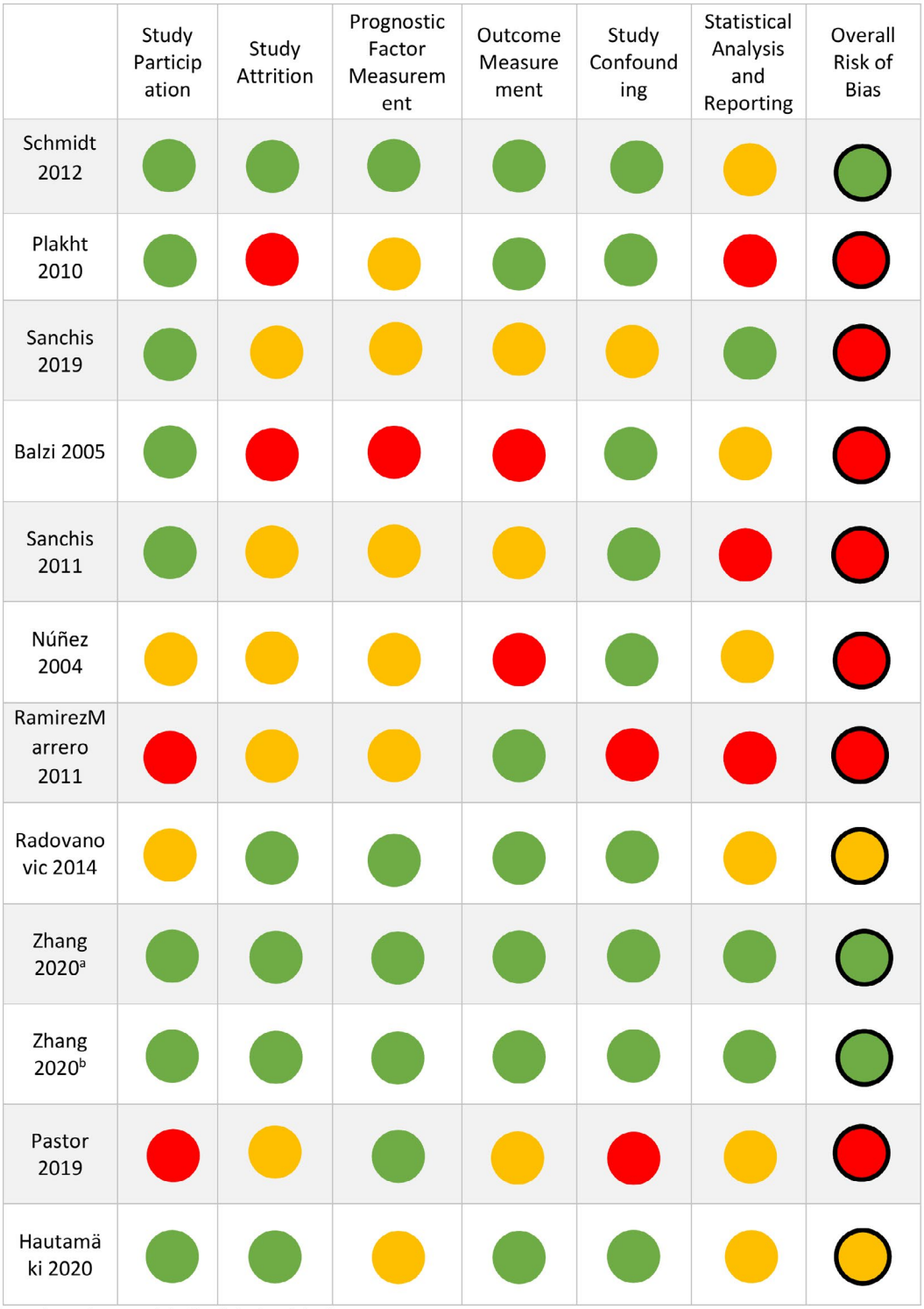
Abbreviations: ACS, acute coronary syndrome; AMI, acute myocardial infarction; MI, myocardial infarction; NA, not available; NSTEACS, non-ST-segment elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

3.3 | Characteristics of comorbidity measures

The details of the comorbidity measures' design, reported outcomes, modelling used and the association of comorbid burden with ACS outcomes across the included studies were summarised in Table 2.

3.3.1 | Comorbidity measures' design

A total of six different types of comorbidity measures were identified in the studies examined: (1) CCI, (2) Soroka Acute Myocardial Infarction (SAMI), (3) Simplified comorbidity measure (SCM), (4)



Low risk (green); moderate risk (yellow); high risk (red).

FIGURE 2 Risk of bias for the included studies according to the Quality In Prognostic factor Studies (QUIPS) tool

Chronic comorbidity score (CS), (5) Simple comorbidity index (SCI) and (6) ECS. These comorbidity measures are summarised in Table S3.

The CCI was the most widely used measure in this review with seven studies[26,27,29,31-34] using CCI to define comorbid burden, with three[26,29,33] presenting use of the original CCI score[12] rather than Deyo modification.[13] Four of these studies[26,27,31,33] computed CCI scores for each patient and categorised the scores into four levels of comorbidity (CCI = 0, 1, 2 or ≥3), one study categorised CCI scores into quartiles,[34] whereas the studies by Ramirez-Marrero[32] and Hautamaki[29] applied CCI scores as a continuous variable. Only one study[28] used the ECS method and categorised ECS scores into

TABLE 2 Summary of measured outcome, comorbid measures used, modelling used, association presented and effect characteristics

Study ID	Outcomes	Comorbidity measure used	prognostic factor/ covariate; type of variable	Modelling	Final prognostic effect estimates for comorbidity measure (unadjusted and adjusted by other covariates)
Schmidt 2012	30-day all-cause mortality	The original CCI (19 conditions)	CCI as prognostic factor. Summary scores as a categorical variable (0, 1, 2, ≥3)	Cox proportional hazard regression	*30-day mortality:* Results from unadjusted models: 1 versus 0: HR = 1.85 (95%CI: 1.73-1.98) 2 versus 0: HR = 2.09 (95%CI: 1.94-2.25) ≥3 versus 0: HR = 2.72 (95%CI: 2.53-2.91) Results from adjusted models: 1 versus 0: HR = 1.35 (95%CI: 1.26-1.45) 2 versus 0: HR = 1.52 (95%CI: 1.41-1.64) ≥3 versus 0: HR = 1.96 (95%CI: 1.83-2.11)
	31-365 days all-cause mortality				*31- to 365-day mortality:* Results from unadjusted models: 1 versus 0: HR = 2.64 (95%CI: 2.42-2.87) 2 versus 0: HR = 3.61 (95%CI: 3.30-3.96) ≥3 versus 0: HR = 5.80 (95%CI: 5.34-6.31) Results from adjusted models: 1 versus 0: HR = 1.83 (95%CI: 1.68-2.00) 2 versus 0: HR = 2.50 (95%CI: 2.29-2.74) ≥3 versus 0: HR = 3.89 (95%CI: 3.58-4.24)
Plakht 2010	1-year all-cause mortality	SAMI (11 parameters)	SAMI as prognostic factor. Summary scores as a continuous variable	Logistic regression	Results from adjusted models: OR = 1.39 (95%CI: 1.33-1.45)
Sanchis 2019	1-year all-cause mortality	SCM (6 comorbidities)	SCM as prognostic factor. Summary numbers of comorbidities as a categorical variable (0-1, 2, ≥3)	Cox proportional hazard regression	No results from unadjusted models. Results from adjusted models: 2 versus 0-1: HR = 1.29 (95%CI: 0.81-2.04) ≥3 versus 0-1: HR = 1.91 (95%CI: 1.20-3.03)
Balzi 2005	1-year all-cause mortality	CS (14 chronic diseases)	CS as a covariate. Summary scores and tertile to 3 categories (cut-off values can vary)	Cox proportional hazard regression	No results from unadjusted models. Results from adjusted models: 2 versus 1: HR = 1.87 (95%CI: 1.04-3.38) 3 versus 1: HR = 2.12 (95%CI: 1.18-3.82)
Sanchis 2011	1-year all-cause mortality	SCI (5 comorbidities)	SCI as prognostic factor. Summary points as a categorical variable (0, 1-2, ≥3)	Cox proportional hazard regression	No results from unadjusted models. Results from adjusted models: 1-2 versus 0: HR = 1.7 (95%CI: 1.0-3.1) ≥3 versus 0: HR = 4.8 (95%CI: 2.7-8.5)
Núñez 2004	30-day mortality or reinfarction	CCI/Deyo (17 comorbidities)	CCI as prognostic factor. Summary scores as a categorical variable (0, 1, 2, ≥3)	Cox proportional hazard regression	*30-day mortality or reinfarction:* No results from unadjusted models. Results from adjusted models: 1 versus 0: HR = 1.69 (95%CI: 1.10-2.59) 2 versus 0: HR = 1.78 (95%CI: 1.08-2.92) ≥3 versus 0: HR = 1.57 (95%CI: 0.87-2.83)
	1-year mortality or reinfarction				*1-year mortality or reinfarction:* No results from unadjusted models. Results from adjusted models: 1 versus 0: HR = 1.62 (95%CI: 1.18-2.23) 2 versus 0: HR = 2.00 (95%CI: 1.39-2.89) ≥3 versus 0: HR = 2.24 (95%CI: 1.50-3.36)

(Continues)

TABLE 2 (Continued)

Study ID	Outcomes	Comorbidity measure used	prognostic factor/ covariate; type of variable	Modelling	Final prognostic effect estimates for comorbidity measure (unadjusted and adjusted by other covariates)
Ramirez-Marrero 2011	Intrahospital-phase mortality	CCI (unknown version)	CCI as prognostic factor. Summary scores as a continuous variable	NA	Unclear whether the results are from unadjusted or adjusted models: *Intrahospital- phase mortality:* OR = 1.6 (95%CI: 1.4-1.8)
	Long-term (24-month) mortality				*Long-term (24-month) mortality:* OR = 1.3 (95%CI: 1.2-1.5)
	Readmission for HF after follow-up				*Readmission for HF:* OR = 1.2 (95%CI: 1.04-1.3)
	MACEs during follow-up				*MACEs during follow-up:* OR = 1.1 (95%CI: 1-1.2)
Radovanovic 2014	In-hospital mortality	The original CCI (19 conditions)	CCI as prognostic factor. For in-hospital mortality: Summary scores as a categorical variable	Logistic regression	*In-hospital mortality:* No results from unadjusted models. Results from adjusted models: 1 versus 0: OR = 1.36 (95%CI: 1.16-1.60) 2 versus 0: OR = 1.65 (95%CI: 1.38-1.97) ≥3 versus 0: OR = 2.20 (95%CI: 1.86-2.57)
	1-year mortality		For 1-year mortality: Summary scores as a continuous variable		*1-year mortality:* No results from unadjusted models. Results from adjusted models: OR = 1.44 (95%CI: 1.36-1.53)
Zhang 2020	In-hospital mortality	CCI/Deyo (17 comorbidities)	CCI as prognostic factor; Summary scores as a categorical variable (0, 1, 2, ≥3); In sensitivity analysis, summary scores as a continuous variable.	Logistic regression	No results from unadjusted models. *In-hospital mortality:* Results from adjusted models: 1 versus 0: OR = 1.31 (95%CI: 1.29-1.34) 2 versus 0: OR = 1.45 (95%CI: 1.41-1.50) ≥3 versus 0: OR = 1.74 (95%CI: 1.68-1.79) OR = 1.13 (95%CI: 1.12-1.14)
	MACCE				*In-hospital MACCE:* Results from adjusted models: 1 versus 0: OR = 1.23 (95%CI: 1.20-1.25) 2 versus 0: OR = 1.35 (95%CI: 1.32-1.38) ≥3 versus 0: OR = 1.70 (95%CI: 1.66-1.75) OR = 1.13 (95%CI: 1.12-1.14)
	Major bleeding				*In-hospital Major bleeding:* Results from adjusted models: 1 versus 0: OR = 1.16 (95%CI: 1.13-1.18) 2 versus 0: OR = 1.33 (95%CI: 1.29-1.37) ≥3 versus 0: OR = 1.64 (95%CI: 1.59-1.69) OR = 1.12 (95%CI: 1.12-1.13)

(Continues)

TABLE 2 (Continued)

Study ID	Outcomes	Comorbidity measure used	prognostic factor/ covariate; type of variable	Modelling	Final prognostic effect estimates for comorbidity measure (unadjusted and adjusted by other covariates)
	Acute ischemic stroke				*In-hospital Acute ischemic stroke:* Results from adjusted models: 1 versus 0: OR = 1.26 (95%CI: 1.21-1.31) 2 versus 0: OR = 1.48 (95%CI: 1.41-1.55) ≥3 versus 0: OR = 2.35 (95%CI: 2.23-2.46) OR = 1.18 (95%CI: 1.17-1.19) OR of Individual comorbidities for each outcome in Supplementary Table S4 in the paper.
Zhang 2020	In-hospital mortality	ECS (30 conditions)	ECS as prognostic factor Summary scores as a categorical variable (<0, 0, 1-5, 6-13, ≥14); Summary number of comorbidity conditions as a categorical variable (0, 1, 2, 3, 4, ≥5) In sensitivity analysis, summary scores and number of comorbidity conditions as a continuous variable	Logistic regression	No results from unadjusted models. *In-hospital mortality:* Results from adjusted models: 0 versus < 0: OR = 1.25 (95%CI: 1.20-1.30) 1-5 versus < 0: OR = 2.16 (95%CI: 2.09-2.24) 6-13 versus < 0: OR = 3.30 (95%CI: 3.18-3.41) ≥14 versus < 0: OR = 4.81 (95%CI: 4.60-5.02) 1 versus 0: OR = 0.95 (95%CI: 0.92-0.98) 2 versus 0: OR = 1.06 (95%CI: 1.02-1.09) 3 versus 0: OR = 1.19 (95%CI: 1.14-1.24) 4 versus 0: OR = 1.36 (95%CI: 1.30-1.41) ≥5 versus 0: OR = 1.65 (95%CI: 1.58-1.72) ECS: OR = 1.08 (95%CI: 1.07-1.09) NEC: OR = 1.11 (95%CI: 1.10-1.12)
	MACCE				*In-hospital MACCE:* Results from adjusted models: 0 versus < 0: OR = 1.11 (95%CI: 1.08-1.14) 1-5 versus < 0: OR = 1.79 (95%CI: 1.75-1.84) 6-13 versus < 0: OR = 2.86 (95%CI: 2.78-2.94) ≥14 versus < 0: OR = 4.65 (95%CI: 4.49-4.82) 1 versus 0: OR = 0.98 (95%CI: 0.95-1.00) 2 versus 0: OR = 1.08 (95%CI: 1.04-1.11) 3 versus 0: OR = 1.22 (95%CI: 1.18-1.26) 4 versus 0: OR = 1.37 (95%CI: 1.32-1.43) ≥5 versus 0: OR = 1.69 (95%CI: 1.63-1.76) ECS: OR = 1.08 (95%CI: 1.07-1.09) NEC: OR = 1.12 (95%CI: 1.11-1.13)
	Major bleeding				*In-hospital Major bleeding:* Results from adjusted models: 0 versus < 0: OR = 0.61 (95%CI: 0.59-0.63) 1-5 versus < 0: OR = 1.10 (95%CI: 1.07-1.14) 6-13 versus < 0: OR = 1.49 (95%CI: 1.45-1.54) ≥14 versus < 0: OR = 2.34 (95%CI: 2.25-2.45) 1 versus 0: OR = 1.12 (95%CI: 1.07-1.16) 2 versus 0: OR = 1.31 (95%CI: 1.26-1.36)

(Continues)

TABLE 2 (Continued)

Study ID	Outcomes	Comorbidity measure used	prognostic factor/ covariate; type of variable	Modelling	Final prognostic effect estimates for comorbidity measure (unadjusted and adjusted by other covariates)
					3 versus 0: OR = 1.58 (95%CI: 1.51-1.66)
					4 versus 0: OR = 1.93 (95%CI: 1.84-2.04)
					≥5 versus 0: OR = 2.59 (95%CI: 2.46-2.72)
					ECS: OR = 1.06 (95%CI: 1.05-1.07)
					NEC: OR = 1.19 (95%CI: 1.18-1.20)
	Acute ischemic stroke				*In-hospital Acute ischemic stroke:*
					Results from adjusted models:
					0 versus < 0: OR = 0.98 (95%CI: 0.92-1.03)
					1-5 versus < 0: OR = 1.50 (95%CI: 1.41-1.58)
					6-13 versus < 0: OR = 3.03 (95%CI: 2.85-3.21)
					≥14 versus < 0: OR = 6.00 (95%CI: 5.61-6.42)
					1 versus 0: OR = 1.28 (95%CI: 1.18-1.38)
					2 versus 0: OR = 1.64 (95%CI: 1.52-1.77)
					3 versus 0: OR = 2.00 (95%CI: 1.84-2.16)
					4 versus 0: OR = 2.31 (95%CI: 2.13-2.51)
					≥5 versus 0: OR = 2.98 (95%CI: 2.73-3.24)
					ECS: OR = 1.10 (95%CI: 1.09-1.11)
					NEC: OR = 1.19 (95%CI: 1.18-1.20)
					OR of Individual comorbidities for each outcome in Supplementary Table 5 in the paper.
Pastor 2019	6-month all-cause mortality	CCI (unknown version)	CCI as prognostic factor; Summary scores as a continuous variable; Summary scores quartile to 4 categories (cut-off values varied, no further information found).	Cox proportional hazard regression	No results from unadjusted models.
					6-month mortality (not complete):
					Results from adjusted models:
					HR = 1.15 (95%CI: 1.06-1.26)
					4 versus 1: HR = 6.19 (95%CI: 2.95-12.95)
	6-month readmissions (NA)				*6-month readmissions(not complete):*
					Results from adjusted models:
					HR = 1.15 (95%CI: 1.06-1.26)
					4 versus 1: HR = NA
Hautamäki 2020	1-month all-cause mortality	The original CCI (19 conditions)	CCI as prognostic factor; Summary scores as a continuous variable; Individual comorbidity conditions	Cox proportional hazard regression	*1-month mortality:*
					Results from unadjusted models:
					HR = 1.40 (95%CI: 1.31-1.51)
					Results from adjusted models:
					HR = 1.14 (95%CI: 1.03-1.25)
	6-month all-cause mortality				*6-month mortality:*
					Results from unadjusted models:
					HR = 1.43 (95%CI: 1.34-1.52)
					Results from adjusted models:
					HR = 1.19 (95%CI: 1.10-1.29)

(Continues)

TABLE 2 (Continued)

Study ID	Outcomes	Comorbidity measure used	prognostic factor/ covariate; type of variable	Modelling	Final prognostic effect estimates for comorbidity measure (unadjusted and adjusted by other covariates)
	2-year all-cause mortality				*2-year mortality:* Results from unadjusted models: HR = 1.45 (95%CI: 1.38-1.52) Results from adjusted models: HR = 1.25 (95%CI: 1.18-1.33) HR of Individual comorbidities for each outcome in Tables 2 and 3 in the paper.

Abbreviations: CCI, Charlson comorbidity index; CI, confidence interval; CS, chronic comorbidity score; ECS, Elixhauser comorbidity score; HF, heat failure; HR, hazard ratio; MACCE, major acute cardiovascular and cerebrovascular events; MACE, major acute cardiovascular events; NA, not available; OR, odd ratio; SAMI, Soroka acute myocardial infarction; SCI, simple comorbidity index; SCM, simplified comorbidity measure.

five groups (ECS < 0, 0, 1-5, 6-13, ≥14) and stratified the number of Elixhauser comorbidities into five groups (0, 1, 2, 3, 4, ≥5). One study[18] developed the SAMI risk score which consisted of 11 parameters. The total score for each patient was calculated to define comorbid burden and used as a continuous variable in the model. The SCM was used as a categorical variable with three levels (SCM = 0-1, 2, ≥3) to define the comorbid burden according to the number of the six comorbidities.[19] A summary CS was computed for each patient by summing disease-specific scores and then divided into a categorical variable with three levels (from CS-1 to CS-3) with increasing comorbid burden.[30] One study[35] stratified patients by summing the total SCI scores into three groups: SCI = 0, 1-2, ≥3.

3.3.2 | Reported outcomes and modelling used

The clinical outcomes reported among the 12 studies varied, with the most frequently reported was mortality at various follow-up periods. One-year all-cause mortality was reported in six studies,[18,19,30,31,33,35] whilst in-hospital mortality was reported in four studies.[27,28,32,33] Other less frequent outcomes in individual studies included: 30-day mortality,[26,29,31] 6-month mortality,[29,34] 2-year mortality,[29,32] and in-hospital MACCE.[27,28] The modelling approaches used to assess the association of comorbidity measures with clinical outcomes were cox proportional hazard regression identified in seven studies[19,26,29-31,34,35] and logistic regression identified in four studies,[18,27,28,33] no information was reported in the study by Ramirez-Marrero (Table 2).

3.3.3 | Synthesising the association of comorbidity measures with reported outcomes

Overall, the associations reported (ORs and HRs, in Table 2) between comorbidity measures and clinical outcomes indicated patients in a higher comorbid group or with higher scores were associated with a higher risk of adverse events. For example, five studies that treated comorbid burden as categorical and reported long-term mortality (≥1 year), indicated the adjusted HRs of the highest comorbid group (vs. the reference group) ranged from 1.9 to 4.8 (95% CIs located between 1.2 and 8.5)[19,26,30,31,35]; for 30-day mortality, two studies suggested the adjusted HRs of the highest comorbid group ranged from about 1.6 to 2 (95% CIs from 0.8 to 2.8)[26,35]; two studies[29,34] that used CCI as continuous scores to predict over 6-month mortality also reported the adjusted HRs of per one-unit increase score ranging from 1.15 to 1.25 (95% CIs from 1.06 to 1.33). In studies using logistic regression models with long-term mortality, two studies that treated comorbidity scores as continuous variables reported ORs between 1.39 and 1.44 (95% CIs from 1.3 to 1.53) per one-unit increase in score.[18,33] For in-hospital mortality, two studies[27,32] that used CCI scores as continuous variable reported that higher comorbid burden was associated with a greater mortality risk (OR 1.6, 95%CI, 1.4-1.8 and OR 1.13, 95%CI, 1.12-1.14), whilst one study[33] that used CCI scores as categorical variable reported that the highest comorbid group had an adjusted OR of 2.2 (95%CI 1.86-2.57) for in-hospital mortality compared to the reference group. The study[28] which used ECS scores to define comorbid burden reported the highest burden group had a 4.8-fold increase in the odds of in-hospital mortality compared to the lowest comorbid group (OR 4.81, 95%CI, 4.60-5.02). In addition to other outcomes, one study[32] reported the associations of MACE (OR 1.1, 95%CI, 1-1.2) and readmission for heart failure (OR 1.2, 95%CI, 1.04-1.3) with CCI scores used as continuous variables. Two studies[27,28] reported that continuous CCI scores and ECS scores were independently associated with increased odds of in-hospital MACCE, major bleeding and acute ischemic stroke (MACCE: OR1.13, 95%CI,1.12-1.14; OR1.08, 95%CI,1.07-1.13). Most studies reported adjusted estimates of the association between CCI score and outcomes while only two studies reported unadjusted estimates[26,29] and the study by Ramirez-Marrero lacked information whether the models were adjusted or unadjusted.

3.4 | Studies that only reported model comparison

We identified 10 studies which only reported model comparisons using different comorbidity measures. Although these studies did

not have information on prognosis as per our protocol, their findings on model comparison are relevant to our review.

Nine studies were published between 1994 and 2014 and one study was in 2020. A retrospective study design was present in eight studies[21,36-40,42,43] while a prospective design was identified in one study[20] and a historical inception cohort design was used in the remaining study.[41] The study population comprised mainly patients with AMI (N = 419 009 in nine studies) and participants with ACS (N = 1202 in one study), while the sample size ranged in the individual studies between 1202 and 162 299. Eight comorbidity measures were used in the studies (Table S4). With different comorbidity measures as prognostic factors, the performances of logistic regressions (nine studies) and cox regression (one study) were assessed and compared. Of eight measures, the most common measures were CCI (nine studies) and ECS (six studies), which were also frequently compared and indicated that ECS outperforms CCI in these studies due to its higher model discrimination. In-hospital mortality was the main outcome in most studies. All the studies employed C-statistic as the method to assess and compare model performance. Five studies considered one or two additional methods including calibration slope, Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), Nagelkerke R-square and G-square statistic.

4 | DISCUSSION

4.1 | Summary of included studies

The aim of the present review was to provide an overview of existing measures used to evaluate comorbid burden in patients with ACS and investigate the prognostic impact of different measures of comorbid burden on ACS outcomes. We reported that the most widely studied comorbidity measure used to investigate the relationship between comorbid burden and outcomes in patients with ACS was CCI. We found that a greater comorbidity burden irrespective of how it was measured/defined was consistently associated with an increased risk of a variety of ACS outcomes including mortality and MACCE. Finally, our review also observed model comparisons using different comorbidity measures which implied ECS might have better performance than CCI.

Our review is the first analysis to study the prognostic impact of a broad range of comorbidity measures in patients with ACS. The 12 identified studies, dated between 2004 and 2020, representing data derived from over 6.5 million patients from diverse healthcare systems with a broad range of comorbidity measures used. Many of the identified comorbidity measures except the CS[30] have been externally validated, for example the CCI and the ECS were described in general medical populations and have been validated extensively in a number of medical conditions[10-13,15,44]; Nonetheless there were drawbacks to these studies. Several studies had selective reporting of results, thereby increasing the difficulty of quality assessment as important information was either omitted or unclear (eg, missing data and adjustment variables).[24] Meanwhile, many of the comorbidity scores were created early using historical datasets with small simple sizes, where the prognostic impact of a particular comorbidity may have been only relevant to the population studied. As patterns of medical diagnosis and treatments evolve, the estimated magnitude and direction of association between comorbidity and adverse outcomes may change. For example, AIDS is scored as +6 points in the CCI score consistent with the poor outcomes of AIDS when the CCI score was developed, even though the longer-term outcomes of patients with AIDS have substantially improved in contemporary clinical practice.[45] In addition, most identified measures apart from CCI and ECS have been merely validated in specific populations and may not be suitable for assessment of prognosis in other groups of patients more widely. Finally, our review showed ECS was not used widely to investigate the association of comorbidity burden with ACS outcomes except one study published in 2019,[28] even though comparative studies suggest that it may be superior in predicting mortality in cardiovascular cohorts.[20,21,36,38] Previously a meta-analysis[17] has summarized the impact of CCI scores on cardiovascular diseases, which showed that a higher CCI score was associated with an increased risk of mortality in ACS patients, with each unit increase of CCI score associated with a 33% increased risk of mortality (RR 1.33, 95% CI 1.15-1.54). While this review quantifies the association of CCI scores with ACS outcomes in a larger number of studies, our analysis provides more granular insights into the impact of other comorbidity measures on ACS-related outcomes and highlighted that regardless of how it was defined, a higher comorbidity burden was associated with an increased risk of mortality or MACE. For example, NSTEACS patients with the highest comorbid burden (SCI ≥ 3) had an adjusted HR of 4.8 (95%CI: 2.7-8.5) for 1-year mortality compared to those with no comorbidities (SCI = 0).[35] Another study using CCI score as a continuous variable also showed NSTEACS patients with a higher comorbidity burden (CCI > 0) were more likely to encounter MACE (OR 1.2, 95%CI, 1.04-1.3).[32]

There are several reasons why ACS patients with greater comorbidity burden have an increased risk of adverse outcomes. A study[33] found that the higher the comorbid burden, the longer the delay between the symptom onset and admission. Besides, the symptoms were less typical and there was higher degree of haemodynamic instability which translated into higher Killip class. The 6-month mortality of ACS patients with Killip class I versus class III/IV is around 4%-5% versus 23%-28%.[46,47] An important therapeutic goal in AMI is rapid coronary reperfusion and current guidelines recommend early routine invasive management particularly for STEMI (in the form of primary PCI) and high-risk NSTEMI presentations.[30] However, as highlighted by Sachis et al, invasive strategies are underused in comorbid patients in the context of ACS.[19] The most consistent finding across the studies identified in our review was the lower rate of utilization of coronary reperfusion therapy (eg, PCI or thrombolysis) among ACS patients with higher comorbidity.[18,27,28,30,33,35] For example, Balzi et al[30] found that the proportion of patients receiving coronary reperfusion therapy reduced as the comorbidity increased, from 78.8% in the group with the least comorbidity to 41.9% in the group with the most comorbidities; two identified studies also

reported that patients in higher CCI and ECS groups were less likely to receive coronary angiography or PCI.[27,28] This phenomenon may be attributed to the perception that patients with high comorbidities do not benefit from invasive management or are poor candidates for revascularization.[35] Furthermore, there is evidence that comorbid patients undergoing coronary revascularisation with PCI are at greater risk from sustaining major bleeding complications and adverse outcomes.[7,44,48]

However, data does not support such a conservative approach to such patients, for example, a prospective study of 1017 NSTEACS patients hospitalized in Spain between 2006 and 2009[35] demonstrated that coronary reperfusion was associated with a better prognosis than conservative therapy and the differences were more marked with increasing comorbid scores. Furthermore, in the sensitivity analysis conducted by Sanchis et al,[19] in-hospital revascularization reduced mortality in both groups of patients with less than three comorbidities and patients with three or more comorbidities. Interestingly, the magnitude of mortality reduction was greater among more comorbid patients (20.3% vs. 10.0%).

A previous cohort study[49] has shown that the inclusion of measures of comorbidity burden to commonly used prognosis scores may improve their performance. The GRACE risk prediction index (GRPI) is a tool that was developed for clinicians to estimate the risk of mortality in ACS patients.[50] A study of 1202 ACS patients[42] reported that the prediction of outpatient mortality or cardiac-related events after discharge was improved when CCI scores were added to models using GRPI. Another study of 29 620 ACS patients from Switzerland from 2003 to 2012 found that an increased comorbidity score (CCI>0) was an independent predictor of mortality despite adjustment for type of ACS and the therapy received.[33]

4.2 | Summary of comparison studies

Among the model comparison studies, studies[20,21,36,38] reported that ECS might perform better than the more widely used measure, CCI in prediction models for ACS-related outcomes. For example, a retrospective study of 144,687AMI patients using administrative data from five countries in 2008-2009 reported that ECS may achieve better discrimination than CCI in the prediction of 30-day mortality[20]; another two retrospective studies[21,38] with a total of 50 479 AMI patients from 1994 to 2001 in California and Canada demonstrated the same conclusion in predicting in-hospital mortality. A study with 8961 AMI patients in 2001-2002 demonstrated the ECS model had the largest C-statistic (best-discriminated ability) in predicting 1-year follow-up mortality.[36] It is noted that, except for one study which was published recently in 2020,[43] four studies that included ECS applied it as separate binary variables in the model rather than using its scoring system due to lack of the weighting algorithm of the original ECS. Meanwhile, those studies also used CCI comorbidities as individual categorical variables instead of its weights that were more commonly used in practice. It is possible this way could cause ECS to have better predictive performance than CCI as ECS contained more conditions than CCI. Whilst ECS may have better discrimination than CCI, it is more complex to calculate than CCI, and so use of such comorbidity scores in clinical practice is often a balance between usability and performance.

4.3 | Potential research interest

Although comparison studies in our review indicated that the Elixhauser method has more discriminative ability for the prediction of outcomes following ACS than the Charlson/Deyo method, most studies used the CCI method to investigate the prognostic impact of comorbidity burden on ACS patients. The ECS method was rarely utilised except in one study published in 2019. Future work is required to study the performance of the ECS in wider ACS populations using routinely collected administrative data in the future. Finally, although all included studies revealed that the risk of adverse outcomes was associated with the increasing comorbid burden, it is unclear whether the ACS patients classified into the comorbid groups using one measure are similarly classified using another comorbidity method. Therefore, it is essential to investigate how the agreement between these comorbidity methods is when classifying patients.

4.4 | Limitations

Our analysis was performed complying with updated guidance[22] of the systemic review for prognostic factor studies. However, we also acknowledge limitations of our review. It only has a small number of studies included, with most of them were considered to be at high RoB based on the assessment of QUIPS. Owing to the heterogeneity of these studies, with substantial differences in modelling approaches, ACS outcomes and coding of comorbidity variables, a quantitative synthesis was not performed.

5 | CONCLUSION

This systematic review paper identified six comorbidity measures, summarised their associations with ACS outcomes and assessed the quality of those studies. We observed that CCI was the most widely used measure of comorbidity burden that was used to explore the relationship between comorbidity burden and ACS outcomes. Despite methodological heterogeneity among the identified studies, the review confirmed that irrespective of how comorbidity burden was defined, higher comorbidity burden or scores were associated with a greater risk of mortality and MACE in patients presenting with ACS. The addition of measures of comorbidity burden may help to optimise risk stratification tools used in clinical practice to guide treatment for patients with ACS.

DISCLOSURES

None declared.

DATA AVAILABILITY STATEMENT

There is no data in this article.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

How to cite this article: Zhang F, Wong C, Chiu Y, et al. Prognostic impact of comorbidity measures on outcomes following acute coronary syndrome: A systematic review. *Int J Clin Pract*. 2021;75:e14345. https://doi.org/10.1111/ijcp.14345