Defining Cardio-renal-metabolic (CRM) Syndrome: A Targeted Literature Review

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INTRODUCTION

- The cardiovascular, renal, and metabolic systems are intricately linked[1]
- Diseases of these systems, such as type 2 diabetes (T2D), chronic kidney disease (CKD), atherosclerotic cardiovascular disease (ASCVD), and heart failure (HF), may have overlapping etiologies and shared risk factors[2]
  - Two or more of these conditions are frequently observed within the same patient[2]
- The interplay between diseases of these systems has been termed cardio-renal-metabolic (CRM) syndrome[3]
- Clinicians are increasingly called upon to adopt integrated care strategies to account for comorbidities and risk factors across all 3 systems rather than managing the individual conditions in isolation[2]
- Despite extensive literature on individual CRM indications and combinations, it is unknown if there is a clear consensus on how CRM syndrome is defined

OBJECTIVE

To conduct a targeted literature review to understand existing literature-based definitions of CRM syndrome and determine if there is a clear consensus on the definitions of CRM syndrome and associated risk factors

ABSTRACT

Background: The cardiovascular, renal, and metabolic systems are intricately linked. Diseases of these systems, such as type 2 diabetes (T2D), chronic kidney disease (CKD), atherosclerotic cardiovascular disease, and heart failure (HF), have overlapping etiologies and shared risk factors, and two or more of these conditions frequently occur in the same patient. The interplay between diseases of these systems has been termed cardio-renal-metabolic (CRM) syndrome.

Methods: A targeted literature review was conducted to identify contemporary definitions of CRM syndrome. The PubMed database and online media were searched for sources published in English between January 1, 2018, and June 1, 2023. Sources were included if they defined CRM syndrome holistically, rather than as individual conditions.

Results: Seventeen sources met the inclusion criteria and included a definition of CRM syndrome. Ten (58.8%) sources described treatment; five (29.4%) reported epidemiology; and three (17.7%) described pathophysiology. Sixteen (94.1%) definitions included kidney conditions defined by estimated glomerular filtration rate (eGFR), including CKD, end-stage renal disease, or decreased eGFR. T2D was the most frequently included metabolic condition (94.1%), with fewer sources including obesity (29.4%) or non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (11.8%). There was greater variability in conditions included in cardiovascular definitions: HF was most common (82.4%), followed by myocardial infarction and stroke (each 41.2%).

Conclusion: Definitions of CRM syndrome were variable, but most definitions included renal impairment and T2D. Clinicians are increasingly called upon to adopt integrated care strategies to account for comorbidities and risk factors across all 3 systems, rather than isolated, individual conditions.

METHODS

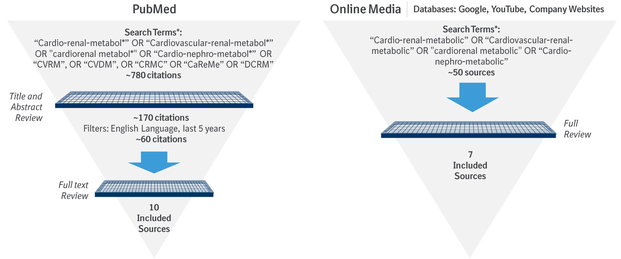
- A targeted literature review was conducted to identify contemporary definitions of CRM syndrome
- A scientific database (PubMed) and online media sources (Google, YouTube, pharmaceutical company websites, etc.) were used to identify sources using search terms such as "Cardio-renal-metabol*", "Cardiovascular-renal-metabol*", "Cardio-nephro-metabol*", "CVRM", etc. *[see Figure 1]*
- Sources were included if they defined the concept of CRM holistically, rather than as individual conditions *[see Table 1]*
- Sources were excluded if they did not define CRM, did not discuss CRM holistically, discussed only CRM in the context of treatment, or were not related to CRM *[see Table 1]*
- The searches were limited to sources published in English from January 1, 2018, to June 1, 2023 *[see Figure 1]*
- The titles and abstracts of all identified citations were reviewed, and full-text/media sources were evaluated for inclusion
- Data were extracted from each included source, including source characteristics (i.e., authors, year of publication, journal, source/study type, funding), and CRM elements (i.e., CRM definitions, risk factors, epidemiology, treatment/management, recommendations) if applicable

Table 1: Screening Criteria

	Inclusion Criteria	Exclusion Criteria
Topic	Defines CRM syndrome	Describes any of the below conditions individually, rather than all 3 conditions combined holistically: • Cardiovascular disease(s) • Renal disease(s) • Metabolic disease(s) Described CRM syndrome in the context of treatment
Study design	• Reviews (including narrative and systematic reviews) • Editorials, Commentaries • Guidelines • Economic analyses and models • Observational studies • Non-randomized and RCT	Non-human studies
Year Published	Published in the last 5 years (2018-2023)	Published prior to 2018
Publication types (PubMed only)	Articles with abstract	Articles without abstract
Language	English	Any other language

RESULTS

Figure 1: Search Terms and Methodology



- Seventeen sources met the inclusion criteria; 10 from searching PubMed and 7 from searching online media databases
- The majority of authors/contributors on included sources were cardiologists and endocrinologists

Table 2: Components of CRM Source Information

CRM component	Number of sources	Key highlights
Treatment/ Management	**10 sources** described CRM **treatment/management** **1 source** included specific treatment/management **recommendations**	• Recommend a **holistic care approach** for managing CRM • Some sources mention **therapy, including SLGT2i** (i.e., empagliflozin, canagliflozin, and dapagliflozin) • **The DCRM Task Force suggests a multispecialty practice** for the management of patients with diabetes, cardiorenal, and metabolic diseases
Epidemiology	**5 sources** included **epidemiology** information	• Indicate **increasing global trend** in the **prevalence** and **incidence** of CRM
Pathophysiology	**3 sources** described CRM **pathophysiology**	• Suggest **pathophysiology leading to CRM disease**

- In addition to defining CRM syndrome, ten (58.8%) sources described CRM treatment/management; five (29.4%) reported on epidemiology; and three (17.7%) described pathophysiology related to CRM syndrome
- For management of CRM, included literature emphasized early intervention focused on implementing formal diagnostic criteria for obesity, metabolic syndrome, diabetes, hypertension, lipid abnormalities, NASH, ASCVD, HF, and CKD, as recommended by the DCRM Task Force
- An endorsement of a holistic, multidisciplinary approach to CRM care is favored over isolated treatment of individual conditions

Figure 2: Source Distribution By Year

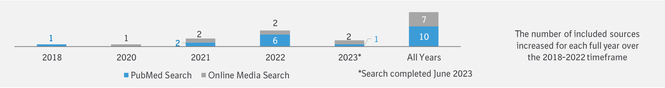
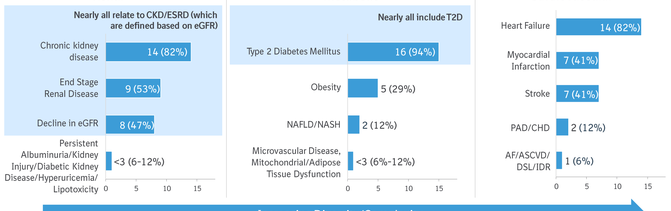


Figure 3: Frequency of Conditions Mentioned in the Included Sources



- Decline in eGFR, CKD, and ESRD generally represent the same process of CKD progression and are included in all but one source
- Diabetic kidney disease shows the inter-relatedness of CRM indications
- T2D is the most consistent indication included in published CRM definitions overall, as well as within the metabolic pillar
- The inclusion of obesity and NASH/NAFLD in definitions suggests potential evolution of the metabolic pillar
- CRM cardiovascular elements included both function-based and ischemic conditions
- Greater balance was observed among the top three indications included under cardiovascular

Note: Individual conditions listed from the sources are not mutually exclusive

For the metabolic component, T2D was the most prevalent indication within CRM definitions (94.1% of sources)

- Fewer sources included obesity (29.4%) or non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NAFLD/NASH) (11.8%)

While the renal components of CRM captured in the literature primarily concentrated on the stages of CKD progression/estimated glomerular filtration rate (eGFR), the cardiovascular aspects of CRM exhibited greater variability.

- Sixteen (94.1%) CRM definitions included kidney conditions related to eGFR, including decreased eGFR or conditions defined by eGFR levels (i.e., CKD and end-stage renal disease)
- There was greater variability in conditions included in cardiovascular definitions: HF was most common (82.4%), followed by myocardial infarction and stroke (each 41.2%)

DISCUSSION

Lack of Consensus on CRM Syndrome Definition

- As demonstrated by the lack of overall literature and consensus on definitions, CRM is continuing to evolve as a holistic concept of disease
- Most CRM definitions focus on the interconnectivity and clustering of multiple cardiovascular, renal, and metabolic indications, but within these core conditions, the individual included disease states vary

Core Components of CRM Syndrome

- The renal pillar showed the least variability, with most CRM definitions relying on eGFR
- T2D was the predominant metabolic parameter identified in CRM definitions, and the development of the holistic CRM syndrome state was often indexed to T2D
- Cardio-related aspects of CRM showed a more balanced – yet limited – distribution across heart failure and ischemic conditions of either the heart or brain

Management of CRM Syndrome

- There is an emerging view within the literature that coordinated, integrated, and patient-centered care should be provided across specialties given the multi-system nature of CRM
- Sources addressing management largely promote the need for early identification of CRM syndrome and a shift from a reactive management strategy to a proactive approach

Following the completion of this review (i.e., in October 2023), two articles published by the American Heart Association (AHA) proposed the existence and concept of cardiovascular-kidney-metabolic (CKM) syndrome that align with the majority of the included definitions in this review[4,5]

- One of these articles summarizes the evidence for the science and clinical management of CKM syndrome and highlights the complexity and interplay of multiple systems, including an emphasis on the need to address the increasing number of patients with CKM syndrome using interdisciplinary collaboration involving pediatrics, primary care, nephrology, cardiology, and endocrinology[4]
- The second article is a Presidential Advisory defining CKM syndrome as a health disorder resulting from connections among obesity, diabetes, CKD, and CVD, including heart failure, atrial fibrillation, coronary heart disease, stroke, and peripheral artery disease. The article also introduces a CKM staging framework that reflects the pathophysiology and spectrum of risks, including a framework for optimizing CKM health by improving education, increasing research investment, addressing social determinants of health, and promoting equitable access to care[5]

SUMMARY & CONCLUSIONS

- The growing number of sources providing definitions for CRM syndrome since 2018 suggests increased emphasis on approaching CRM holistically
- The identified literature suggests that cardiologists and endocrinologists are at the forefront of shaping the narrative surrounding CRM
- Definitions of CRM syndrome were variable, but most definitions consistently included renal impairment and T2D
- CRM syndrome may evolve from individual indications, with multiple cardio-renal-metabolic risk factors potentially contributing to disease development and progression
- Clinicians are being called upon to adopt integrated care strategies across all three systems, rather than the management as individual conditions in isolation
- Notably, a consensus definition for CRM syndrome had not yet materialized at time of review, underscoring the ongoing complexity and evolution of this field
- Achieving a more diverse and widely accepted definition of CRM syndrome is needed to embrace its holistic management

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Abbreviations: AF: Atrial fibrillation; ASCVD: Atherosclerotic cardiovascular disease; AHA: American Heart Association; CHD: Coronary heart disease; CKD: Chronic kidney disease; CKM: Cardiovascular-kidney-metabolic; CRM: Cardio-renal-metabolic; DCRM: Diabetes, CardioRenal Metabolic Diseases; HF: Heart failure; DSL: Dyslipidemia; IDR: Impaired diastolic relaxation; eGFR: estimated glomerular filtration rate; ESRD: End-stage renal disease ; NAFLD: Non-alcoholic fatty liver disease ; NASH: Non-alcoholic steatohepatitis; PAD: Peripheral Arterial Disease; RCT: Randomized controlled trial; SGLT2i: Sodium-glucose co-transporter 2 inhibitor; T2D: Type 2 diabetes

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