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Anxiety and depression in cardiac amyloidosis: a systematic review

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ABSTRACT

Objectives Cardiac amyloidosis (CA) is a rare and underdiagnosed disease associated with a high mortality rate. Although, in the last decade, there has been increasing attention in the literature to the relationship between CA and psychological distress in patients, the evidence on this association has not yet been systematised. Therefore, this study aims to fill this gap.

Design Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, a systematic review was conducted.

Data sources PubMed, ScienceDirect, Scopus and Web of Science were searched, with the last update conducted on 23 September 2024, and no time restrictions were applied.

Eligibility criteria Studies had to meet the following inclusion criteria to be included: (1) original quantitative research; (2) published in peer-reviewed journals written in English; (3) explore and report the relationship between CA and psychological distress or compare a clinical group with a control group and (4) investigate psychological distress through reliable and validated measures.

Data extraction and synthesis One author extracted the data, which was then double-checked by another, and data were reported both in tabular and textual form. The included studies were critically evaluated using the Appraisal Tool for Cross-Sectional Studies.

Results Through the research process, a total of 14 articles were selected. The quality assessment scores ranged from 12 to 18 (M=16.21±1.42). Overall, the results underline a significant presence of psychological distress in patients with CA. Moreover, while disease severity was not found to be associated with psychological distress in CA patients in all studies considered, more heterogeneous results emerged regarding the association between the severity of cardiac symptoms and psychological distress.

Conclusions Results suggest that psychological distress is an important aspect to be considered when dealing with CA patients. Integrating psychological assessment and support may improve patient outcomes by reducing disease burden and enhancing treatment adherence.

PROSPERO registration number CRD42023446913.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first systematic review focused specifically on anxiety and depression in cardiac amyloidosis, conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and registered on PROSPERO.
⇒ The quality of the included studies was critically assessed using the Appraisal Tool for Cross-Sectional Studies.
⇒ All included studies used a cross-sectional design to assess the psychological aspects related to cardiac amyloidosis, preventing the determination of the direction of this association.
⇒ The included studies used heterogeneous psychological assessment tools, limiting comparability of the results.

INTRODUCTION

Amyloidosis is a group of rare diseases characterised by the presence of a protein which tends to assume an anomalous conformation depositing in the extracellular space of tissues and organs,[1] including the heart.[2 3] Specifically, there are two main forms of amyloidosis capable of inducing clinically relevant cardiac involvement: light chain cardiac amyloidosis (AL-CA) and transthyretin amyloidosis CA (ATTR-CA).[4] In AL-CA, amyloid fibrils come from an excess of light chains of a monoclonal immunoglobulin. On the other hand, ATTR-CA is caused by the misfolding and deposition of transthyretin (TTR), a protein produced primarily by the liver, and it is further subdivided into two forms: hereditary or variant (ATTRv-CA) and wild-type (ATTRwt-CA). ATTRv-CA is derived from one of more than 120 mutations in the TTR gene (chromosome 18) and, although the mutation is present from birth, the protein starts to misfold and deposit in tissues after several decades (from the age of 30–60 according to different mutations and geographical area).[5] On the contrary, in ATTRwt-CA, there are no mutations in the TTR gene, and the protein seems to acquire instability and predisposition to aggregation due to some process related to ageing, although, to date, there is no clear explanation of this mechanism. Although CA is considered a rare disease, several reports demonstrated an increase in diagnosis in recent years is mainly due to increased disease awareness and the availability of refined diagnostic tools.[6–8] The diagnostic process can be difficult due to the fact that the majority of patients with CA

initially present non-specific clinical manifestations such as fatigue, peripheral oedema, weight loss and orthostatic hypotension.[9 10] Therefore, the patient diagnostic journey can be long, taking up to 2 years between the onset of symptoms to the formulation of diagnosis.[11] Therefore, it is essential to increase the knowledge of CA red flags and increase disease awareness in order to improve the clinical outcomes by giving timely diagnosis whenever red flags are present.[12]

From what has been analysed so far, it is not surprising that CA is a disease that strongly affects the state of health of patients from various points of view. In fact, cardiac symptoms such as dyspnoea, orthopnoea and fatigue not only affect prognosis but also involve severe physical and functional impairments that affect daily activities and which, in turn, can substantially reduce the patient's quality of life.[13 14] Furthermore, in the last decade, there has been increasing attention on the relation that CA can have with the psychological distress of patients, predominantly in terms of anxiety and depression, in line with studies showing high rates of such conditions in patients with different types of cardiovascular disease.[15–17] Specifically, the attention of researchers and clinicians has focused on the relationship that psychological distress can have with cardiac symptoms in CA patients, both objective and subjective. For example, Ponti *et al*[18] pointed out that when patients with ATTR-CA experienced severe anxiety and/or depression, they tended to overestimate their subjective perception of the severity of their heart failure (HF) as measured with the Kansas City Cardiomyopathy Questionnaire,[19] a common instrument to assess the perceived burden of HF symptoms. This, in turn, makes their self-assessment of cardiac symptoms with patient-reported outcome scales unreliable and not corresponding to objective heart failure parameters. Moreover, Smorti *et al*[20] pointed out that in patients with AL-CA, depression levels were significantly influenced by the severity of cardiac symptoms. These results, in addition to highlighting a general psychological distress in CA patients, raise important reflections on the direct management of patients from a medical point of view.[18] Indeed, in the specific context of pharmacological clinical trials that use the subjective perception of the severity of symptoms as endpoints, such biases associated with the presence of high levels of anxiety and/or depression may hinder a reliable assessment of the severity of symptoms in relation to the objective characteristics of cardiac disease. Therefore, taking into consideration, evaluating and adequately treating not only the physical but also the psychological well-being of patients with CA turns out to be extremely important for at least two aspects. On the one hand, it allows patients to enjoy greater well-being in the round; on the other hand, it makes the objective assessment of cardiac symptoms more accurate and reliable, allowing for better management also thanks to the possible participation in clinical trials.[18] In addition to the above, receiving a diagnosis of CA or being a carrier of a genetic mutation—in the case of ATTRv-CA—with the associated risk of developing a disease in the future and transmitting it to the offspring, has a non-negligible psychological impact both on patients and their families.[21 22]

In light of the above, it is important to consider that a bidirectional relationship may exist between CA and psychological distress. On one hand, anxiety and depression can negatively influence self-care behaviours, medication adherence and illness perception, thereby potentially worsening clinical outcomes. On the other hand, the debilitating nature of CA—including progressive heart failure symptoms, diagnostic delays and limited treatment options—may itself trigger the onset of depressive and anxious symptoms. Furthermore, it is plausible that different types of CA may have distinct psychological impacts. For instance, AL-CA, due to its rapid progression and poorer prognosis,[23] may provoke more severe distress. ATTRv-CA may impose an emotional burden related to the hereditary transmission of the disease and the perceived risk of developing symptoms in the future,[21 22] while ATTRwt-CA, typically affecting older adults, may be accompanied by age-related stressors such as frailty and cognitive decline.[24]

Overall, significant advances in understanding CA have been made in recent years, leading to a thorough reformulation of its clinical significance.[10] Furthermore, improving our understanding of the relationship between CA and psychological distress is essential for better patient management. However, to our knowledge, there is currently no systematic literature review on the association between CA and psychological distress (ie, anxiety and depression). Therefore, our proposal is to present the first systematic review of literature that synthesises the evidence available on this topic.

METHOD

This systematic review was conducted in compliance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines[25] and the protocol was registered on PROSPERO (CRD42023446913).

Eligibility criteria

To be included, studies had to meet the following inclusion criteria: (1) original quantitative research; (2) published in peer-reviewed journals written in English; (3) explore and report the relationship between CA and psychological distress or compare a clinical group with a control group and (4) investigate psychological distress through reliable and validated measures.

Information sources and search strategies

Two authors (SG and LP) conducted the systematic literature search on 15 June 2024, updating it for the last time on 23 September 2024, with no time restrictions. The full search terms used in this study are presented in online supplemental table 1. Briefly, the following databases were searched: PubMed, ScienceDirect, Scopus and Web

Of Science. The search strategy was narrowed down to Titles, Abstracts and Keywords and included the following search string: "cardiac amyloidosis" AND ("psycholog*" OR "psychiatr*" OR "mental" OR "emotional" OR "burden" OR "depression" OR "anxiety" OR "distress" OR "wellbeing" OR "well-being" OR "quality of life"). The references list of the collected articles was also scanned to identify potential additional articles.

Identification, selection and quality assessment of studies

First, two authors (SG and LP) conducted independent research on the databases mentioned above. Subsequently, duplicates were removed, and the titles and abstracts of the remaining records were double screened. Articles deemed unsuitable by both reviewers (based on title and abstracts) were excluded. Any conflicts between the two authors were resolved by a third author (MS). After this preliminary screening, records were examined for eligibility assessment using full texts. Even in this case, two authors (SG and LP) independently conducted the eligibility assessment and resolved any conflicts with the help of a third author (MS). All studies that met the inclusion criteria were reviewed for data extraction.

Subsequently, the included articles were critically evaluated using the Appraisal tool for Cross-Sectional Studies tool,[26] a tool consisting of 20 items with a 3-point Likert response (yes=1, no=0, don't know=0) aimed to evaluate the quality of reporting (7 items), study design quality (7 items) and the possible introduction of biases in the study (6 items). This tool provides a subjective quality score generated by the sum of scores obtained, ranging from 0 to 20, in which scores from 0 to 7 indicate a low quality, from 8 to 14 indicate a medium quality and from 15 to 20 indicate a high quality.[27]

Data extraction

One author (SG) extracted the data, which was then double-checked by another (LP). The following data were extracted for each selected study: (1) author(s) and year of publication; (2) country; (3) study design; (4) type of CA considered; (5) characteristics of the sample; (6) psychological dimensions considered and relative measures and (7) key findings.

Patient and public involvement

None.

RESULTS

Results of the selection process

The details of the selection process are illustrated in figure 1.

The research process of the studies through the databases has led to the identification of 718 records. Subsequently, after removing the duplicates (n=315), the titles and abstracts of the remaining records (n=403) were double screened. Based on the title and the abstracts, studies deemed not suitable by both authors were excluded (n=225). Following this preliminary screening, 178 full-text records were examined for eligibility assessment. Through this process, 11 articles were selected and, through the handsearching of references, a further 3

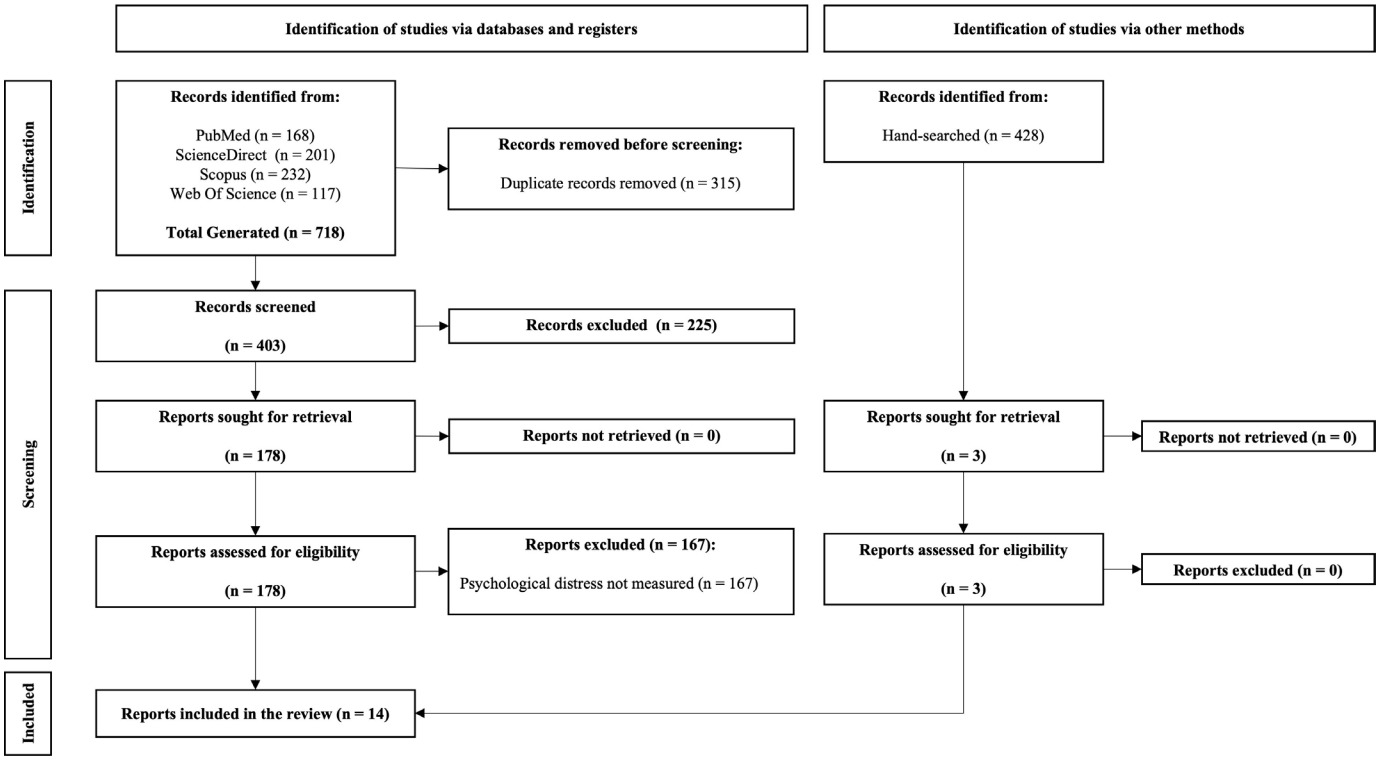

Figure 1 PRISMA flow chart depicting the study selection process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

articles were additionally identified. Therefore, the entire selection process has led to the identification of a total of 14 articles satisfying the inclusion criteria of this systematic review.

Characteristics of studies

Online supplemental table 2 reports the quality assessment of the 14 selected studies.

For individual studies, the quality assessment scores ranged from 12 to 18 (M=16.21, SD=1.42), with 13 studies scoring in the high range of quality and one in the medium range. Overall, the main limitations of the included studies were that they did not adequately justify or clarify their sample size (question 3) and that they did not address and classify non-responders (questions 7 and 13).

Data extracted from the 14 studies selected for this systematic review are shown in online supplemental table 3.

Almost half of the studies (n=6) were conducted in Italy, three in France, one in USA and Spain simultaneously, and one each in USA, Austria, Republic of Korea and the Nordic countries (ie, Denmark, Norway, Sweden and Finland). 12 studies adopted a cross-sectional design while the remaining 2 adopted a longitudinal design. However, as regards the two studies with longitudinal design, one[28] investigated the safety and efficacy of administration of a drug (ie, riociguat), while the other[29] did not investigate the changes in psychological aspects over time. Therefore, the baseline data from these two studies were extracted and interpreted as cross-sectional. Overall, the 14 studies covered 2730 participants (M=195), with sample sizes ranging from 13 to 1226. As for the type of CA considered, 10 studies considered ATTR-CA (8 ATTRwt-CA and 6 ATTRv-CA) while 5 studies considered AL-CA. Specifically, five studies considered both ATTRv-CA and ATTRwt-CA,[18 21 28 30 31] four only the AL-CA,[20 32–34] two only the ATRTwt-CA,[35 36] two the ATTR-CA in general[22 29] and one both forms of ATTR-CA (ATTRv-CA and ATTRwt-CA) and AL-CA.[37]

The measures used in the studies, the constructs they assessed and the frequency of their use are listed in table 1.

As shown, all the studies have investigated anxious and depressive symptoms with different measures. However, four studies have used the EuroQol-5 Dimension (EQ-5D),[38] a self-report measure that assesses anxiety and depression as a single dimension and one referred to the International Classification of Diseases, 10th Revision (ICD-10)[39] categorising anxiety, depression and insomnia as a single category, without therefore being able to grasp the peculiarities of the specific manifestations of anxiety and depression in patients with CA.

Main findings

Depression

Depression was the most investigated dimension, with 11 studies included, and there is a general consensus that it is a highly widespread condition in patients with CA—independently from the specific typology. In particular, four studies measured depression in patients with AL-CA, and whereas one study found that 37% of patients had at least one depressive symptom,[32] two studies showed that 100% of patients were classified as 'clinical' depressed.[20 33] Instead, seven studies investigated depression in patients with ATTR-CA and found a prevalence ranging from 10.70% of patients reported to have any degree of depression[30] to 49% of patients at risk of depression.[35]

In addition, the results showed that the severity of the disease, evaluated with different methodologies such as the National Amyloid Centre score for ATTR-CA and the Mayo staging system for AL-CA, was not associated with depression, neither in AL-CA[20] nor in ATTR-CA.[21 30 31 35]

Table 1 Measurement instruments and constructs listed in the included studies

Measures	Constructs	Studies	No of studies
36-item Short Form General Health Survey	Anxiety and depression separately	Shu *et al*[32]	1
Centre for Epidemiological Study–Depression Scale	Depression	Smorti *et al*[20]; Smorti *et al*[33]; Smorti *et al*[34]	3
EuroQol-5 Dimension (EQ-5D) and variants (EQ-5D-3L and EQ-5D-5L)	Anxiety/depression as a unitary dimension	Damy *et al*[37]; Duca *et al*[28]; Eldhagen *et al*[30]; Stewart *et al*[22]	4
Geriatric Depression Scale	Depression	Broussier *et al*[35]; Broussier *et al*[36]	2
Hospital Anxiety and Depression Scale	Anxiety and depression separately	Fumagalli *et al*[31]; Ponti *et al*[18]; Smorti *et al*[21]; Stewart *et al*[22]	4
International Classification of Diseases 10th Revision	Depression/anxiety/insomnia as a unitary dimension	Jang *et al*[29]	1
Major Depression Inventory	Depression	Eldhagen *et al*[30]	1
State-Trait Anxiety Inventory	Anxiety	Smorti *et al*[20]; Smorti *et al*[34]	2

EQ-5D-3L, EQ-5D-3 Level.

In contrast, all studies considered found a positive association between depression and the cardiac symptom severity, both in AL-CA[20 21] and ATTR-CA,[30 31] evaluated with the New York Heart Association classification system. Furthermore, greater symptom severity was found to be a significant predictor of depressive symptomatology in both AL-CA[20] and ATTR-CA.[21] However, it should be noted that in AL-CA the direct effect of the symptoms severity on depression is no longer significant when considering possible mediating variables, such as coping strategies[33] or life satisfaction.[34]

Furthermore, depression in patients with ATTR-CA was associated with a perception of worse social support by caregivers—but not with conflict towards them[31]—as well as with a worse subjective perception of symptoms severity.[18] This last result turns out to be important considering that Ponti *et al*[18] have also found that the severity of the symptoms self-reported by the patient is reliable, that is, that it coincided with the severity of the objective parameters, only in the presence of mild or medium depressive symptoms.

Anxiety

Anxiety was investigated by six studies, and the results highlight its high prevalence in patients with different manifestations of CA. In particular, three studies measured anxiety in patients with ATTR-CA highlighting a prevalence ranging from 28%[18] to 33%,[21] while three studies in patients with AL-CA found a prevalence ranging from 46.70%[32] to 100%.[20]

Regarding the association between anxiety and severity of the disease, only two studies have investigated this aspect, finding no statistically significant associations either in AL-CA[20] or in ATTR-CA.[21] Moreover, regarding the association between anxiety and symptom severity, this has not emerged in patients with ATTR-CA.[25] In contrast, it was found in patients with AL-CA even when considering the mediating role of other variables, such as life satisfaction.[34] However, Smorti *et al*[20] have not found that anxiety levels are influenced by cardiac symptom severity.

Finally, anxiety in patients with ATTR-CA was associated with a worse subjective perception of symptoms severity, and, similarly to what has already been reported for depression, Ponti *et al*[18] have found reliably the severity of the symptoms self-reported by the patient only in the presence of mild or medium depressive symptoms.

Anxiety/depression

As previously mentioned, five studies have investigated anxiety and depression as a unitary dimension. Only one study investigated this aspect in AL-CA, showing that 47% and 5% of patients reported small/moderate and severe problems of anxiety/depression, respectively.[37] On the contrary, all five studies considered ATTR-CA, highlighting how anxiety and depression are highly present in these patients, with a prevalence ranging from 44%[29] to 50%.[28] Furthermore, no differences emerged in the levels of these problems with respect to the two different types of ATTR-CA (ie, hereditary and wild-type).[30] Specifically, Damy *et al*[37] found that small/moderate anxiety/depression problems were present in 59% and 48% of patients with ATTRv and ATTRwt, respectively, while 8% and 5% had serious problems.

DISCUSSION

Psychological distress appears to play a significant role in cardiovascular disease.[15–17] However, only in the last decade has this aspect been considered with regard to CA, a rare and underdiagnosed disease associated with a high mortality rate[5 39 40] that has a significant psychological impact on both those affected but also their families.[21 41] Nevertheless, to our knowledge, no previous systematic review of literature has addressed the relationship between CA and psychological distress. Therefore, this study aims to fill this gap by offering a systematic review of literature that synthesises the evidence available on this topic. Overall, although the vast majority of included studies did not adequately justify sample size, nor address and classify non-responders, the quality assessment revealed a general low risk of bias of the included studies since they all showed a high quality, with the exception of one, which nevertheless reported a medium quality.[22] It is, therefore, possible to confirm that the results of this systematic review are suitable to provide evidence-based conclusions.

Generally, the results from the 14 studies included in this systematic review have confirmed the presence of a high level of psychological distress in patients with CA, regardless of the type investigated. In particular, all the studies have taken into consideration anxiety and/or depression. For AL-CA, studies have shown that in some circumstances, clinical levels of anxiety[20] and depression[20 33] may occur in all patients—that is, 100%—suffering from this disease. In contrast, high levels of depression and anxiety in ATTR-CA were found in 33%[21] and 49%[35] of patients, respectively. This higher prevalence of psychological distress in patients with AL-CA than those with ATTR-CA may be due to the fact that the former is the most severe form, with the most aggressive progression and the worst prognosis.[5 42]

However, no studies have so far examined and compared patients with different types of CA from a psychological perspective, and therefore, it is possible to advance only speculations; this discrepancy could simply be linked to the use of different measures to investigate psychological distress using different instruments and cut-offs.

Just as the high prevalence of psychological distress in CA is confirmed by all the studies, there is also general agreement regarding the absence of its relationship with the severity of the disease regardless of the type of CA. Indeed, disease severity was not found to be associated with depression neither in ATTR-CA[30 31 35] nor in AL-CA.[20] On the same line, no associations were found between the severity of the disease and anxiety in ATTR-CA[21] and AL-CA.[20] However, this is not surprising since the severity

of the disease is a dimension that is assessed by staging systems (National Amyloid Centre score and the Mayo staging system) based on laboratory parameters and does not measure the perception of the disease from the point of view of the patient.

Less homogeneous conclusions can be drawn regarding the association between the severity of cardiac symptoms and psychological distress, as the analysed studies have shown mixed results, especially when considering AL-CA. In fact, with regard to ATTR-CA, all the studies taken into consideration agree that there is a significant relationship between the severity of cardiac symptoms with depression[21 30 31] but not with anxiety.[21] On the contrary, as far as AL-CA is concerned, although Smorti *et al*[20] found that the severity of cardiac symptoms is the strongest predictor of depressive symptomatology, subsequent studies have shown that this effect is less evident when other variables such as coping strategies[33] or life satisfaction[34] are taken into consideration. Conversely, one study showed that the severity of cardiac symptoms would predict anxiety above and beyond other variables such as life satisfaction,[34] although one study found no such association.[20]

Taken together, these findings also raise the possibility that psychological distress in CA patients may be more strongly linked to the burden of symptomatic cardiac impairment rather than to disease-specific features of amyloidosis itself. Indeed, it is plausible to assume that the severity of heart failure—regardless of its underlying aetiology—exerts a non-specific influence on anxiety and depression. Considering this speculation, future studies should include comparison groups with other forms of cardiac disease to clarify whether the psychological burden is uniquely elevated in CA or reflects broader patterns associated with advanced cardiac dysfunction in line with the results of Broussier *et al*.[36]

Figure 2 provides a summary of the main aspects highlighted in this study.

Despite making a significant contribution to our understanding of the connection between CA and psychological distress, the present systematic review has some limitations. First of all, because we only included studies written in English, we were unable to take into account any noteworthy contributions written in other languages. Second, since the current review is solely based on cross-sectional studies, it was unable to determine the direction of the association between CA and psychological distress. In fact, it is reasonable to assume that the presence of anxious and/or depressive symptomatology may strengthen and exacerbate the severity of perceived cardiac issues which initially contributed to the onset of such mood deflection, resulting in a vicious circle. Longitudinal studies are, therefore, crucial in this field of research. A further limitation that needs to be considered is linked to the fact that some studies used measures that investigated anxious and depressive symptomatology as a single construct (eg, EQ-5D) without realising the substantial difference between these two types of psychological distress.[43 44] Moreover, one study[45] used the ICD-10 criteria to categorise the psychological distress of the participants in terms of a single dimension labelled 'depression/anxiety/insomnia', making it impossible not only to disentangle the specific features of anxiety and depression, but also to differentiate them from insomnia symptoms. Linked to the previous limitations, a further limitation can be

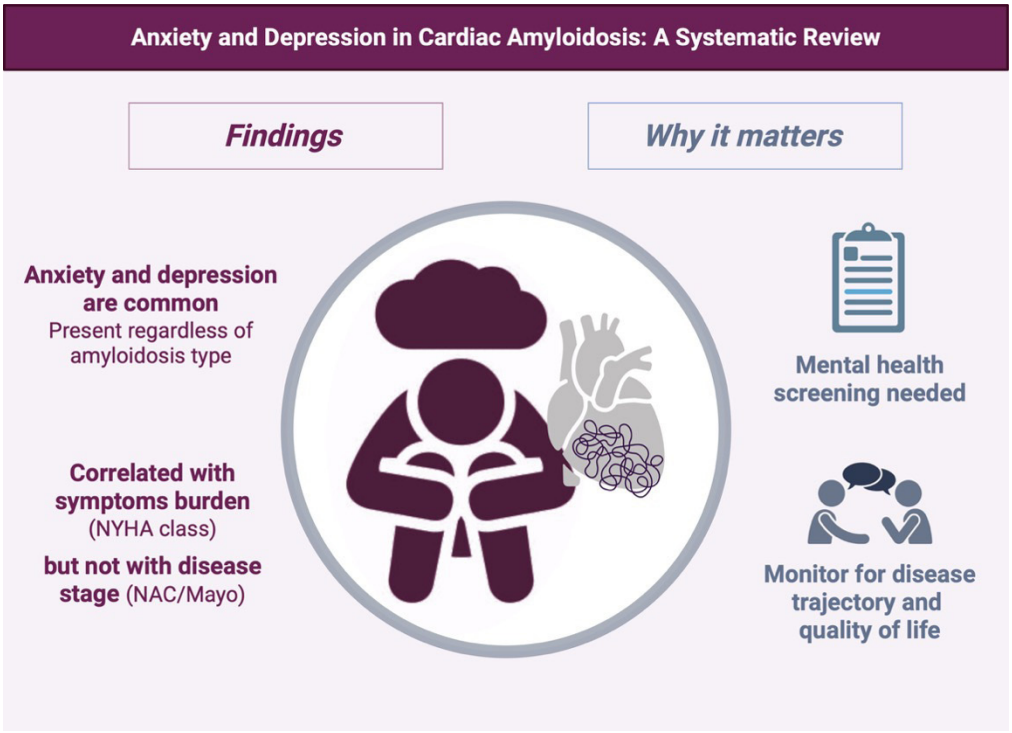

Figure 2 Main findings of the systematic review. NAC, National Amyloid Centre; NYHA, New York Heart Association.

seen in the fact that different measures have been used to investigate psychological distress, and this could partly explain the heterogeneity of the results. In fact, it should be noted that in a total of 14 included studies 8 different measurements were used (see table 1). Moreover, the studies included rely on self-report measures to assess psychological distress, which is prone to inaccuracies and potential biases, such as social desirability and negative affective bias,[46] which may hinder the interpretation of the findings. Therefore, results are to be important that future studies used other data collection methodologies such as clinical interview to overcome defensive and response biases. Furthermore, another important limitation is that none of the included studies considered whether participants were in a phase of acute decompensation or in a clinically stable condition in relation to psychological distress. This lack of information prevents a meaningful differentiation between patients experiencing acute clinical deterioration—often associated with hospitalisation and more severe psychological burden—and those with a more stable outpatient status.[47 48] Since clinical parameters, prognosis and psychological responses may vary substantially depending on the clinical phase of the disease (acute vs chronic), future studies should systematically report and account for this aspect. Addressing this distinction would allow for more accurate interpretations of the emotional and psychological impact of CA and would enhance the applicability of findings in diverse clinical settings. Finally—and particularly relevant for the purposes of this review—no study has explored the psychological distress associated with the CA, taking into account its various types. In fact, although AL-CA turns out to be the most severe and with the worst prognosis,[5 42] the emotional impact of ATTR-CA is not to be ignored. For example, ATTRv-CA, due to its hereditary nature of disease, may be associated with an emotionally impacting load—such as guilt, anxiety and stress—related to the possibility of transmitting the genetic mutation to offspring.[21 22]

Notwithstanding these limitations, this systematic review of literature seems to suggest that psychological distress—in terms of depressive and anxious symptoms—is an aspect to be taken into account when dealing with CA patients. Therefore, it would be desirable that in the CA referral centres the psychological distress of patients should also be taken into consideration, and not just the physical one. A specific psychological evaluation carried out by trained healthcare personnel would in fact be of help in identifying those patients with psychopathological difficulties in order to prevent and deal with any complications linked to the manifested psychological distress as quickly as possible. Indeed, psychological support may be able to lessen the disease burden, enhance quality of life and increase adherence to the treatment of patients.

Contributors Conceptualisation: SG, LP, MS and FC. Methodology: SG, LP and MS. Formal analysis and investigation: SG, LP and MS. Writing–original draft preparation: SG. Writing–review and editing: LP, MS and FC. Supervision: FC. Guarantor: FC.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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