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# Psychological distress, understanding of cancer and illness uncertainty in patients with Cancer of Unknown Primary

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## Abstract

**Objective:** Patients diagnosed with Cancer of Unknown Primary (CUP) experience high levels of psychological distress and report poor understanding of their cancer. We aimed to investigate: (1) if CUP patients with poorer understanding of their cancer diagnosis and testing experience more symptoms of psychological distress than those with better understanding; (2) if the relationship between patients' understanding of their cancer and psychological distress is mediated by illness uncertainty; and (3) explore whether patients' degree of understanding of their cancer can be predicted by clinical and socio-demographic factors.

**Methods:** 209 CUP patients completed a questionnaire measuring anxiety, depression, illness uncertainty, fatigue, pain, sleep and understanding of their cancer. Using an *a priori* theoretical framework, we employed structural equation modelling to investigate predictors of patient's understanding of their cancer and psychological distress and the relationships between understanding, illness uncertainty and distress.

**Results:** The structural equation model displayed good fit indices and supported the hypothesised relationship of patient's understanding of their cancer and the extent of psychological distress, which was mediated via illness uncertainty. Physical symptoms were positively associated with psychological distress and illness uncertainty. Younger age was predictive of lower patient's understanding of their cancer and higher levels of psychological distress.

**Conclusions:** Patients with CUP, particularly those who are younger and experiencing more physical symptoms, report higher levels of psychological distress and may require additional mental health support. Our findings highlight a need to improve CUP patient's understanding about their illness, which could help reduce their illness uncertainty and alleviate psychological distress.

Linda Mileshekin and Penelope Schofield contributed equally as senior authors

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**KEYWORDS**

cancer, illness uncertainty, oncology, psycho-oncology, psychological distress, understanding of cancer, unknown primary tumour site

## 1 | INTRODUCTION

Cancer of Unknown Primary (CUP) is one of the most understudied and most difficult to manage malignancies. Patients are diagnosed with CUP when distant metastatic disease is detected but no primary tumour can be identified following clinical and pathological investigations.<sup>1,2</sup> Although CUP ranks as the fourth most common cause of cancer deaths worldwide, psychological distress and psychosocial needs of CUP patients remains poorly understood, with only a handful of studies published.<sup>2-5</sup> In one study, 40% of CUP patients had clinically relevant depressive symptoms, which was significantly higher than patients with other metastatic cancers of known primary type.<sup>4</sup> CUP patients also displayed higher levels of anxiety, somatization, and overall psychological distress.<sup>4</sup> It is critical to understand more about psychological distress experienced by CUP patients, including modifiable demographic, clinical, and psychological predictors so that clinical interventions can be developed.

### 1.1 | Predicting psychological distress

Patients' understanding of their cancer diagnosis provides a sense of control and empowerment, resulting in the reduction of uncertainty and psychological distress.<sup>6-8</sup> The link between illness uncertainty and psychological distress has been well documented in patients diagnosed with different cancer types including breast, prostate, colorectal and blood cancer<sup>9-12</sup> but not in CUP. The unique characteristic of CUP is that patients must deal with diagnostic uncertainty, the unpredictability of their prognosis, and limited treatment options.<sup>2,3,5</sup> While clinicians recognize the need to inform their patients about their illness, they are faced with a paucity of definitive answers and find the communication challenging.<sup>5,13</sup> Some oncologists find it challenging and uncomfortable to communicate the diagnostic uncertainty when talking to their CUP patients,<sup>14</sup> and this lack of certainty and understanding is echoed in reports from patients themselves. A recent large-scale national study of cancer patients reported experiences of care conducted on more than four thousand UK participants revealed that those with CUP were less likely to report a complete understanding of the explanation provided by their doctors about their illness than non-CUP patients.<sup>15</sup> More than 30% of CUP patients also reported they did not receive sufficient information about their cancer nor did they understand their diagnosis.<sup>15</sup> A small qualitative study similarly revealed CUP patients often feel as if they have not been provided with a clear diagnosis and seek information about the illness by themselves, which highlights the central role for understanding and uncertainty in the experiences of CUP patients.<sup>5</sup>

This study also indicated that uncertainty among CUP patients may play a role in their psychological distress.<sup>5</sup>

### 1.2 | Predicting understanding

Existing evidence indicates a third of CUP patients have low understanding of their cancer,<sup>15</sup> and therefore it is important to identify contributing factors to develop targeted resources and tailored communication strategies to improve patients' understanding. Aging and age-related cognitive decline contribute to the impairment in memory and learning,<sup>16,17</sup> which could possibly interfere with the patients' understanding of their cancer. Emerging research focussing on cancer patients from culturally and linguistically diverse backgrounds for whom English is not a first language suggests that misunderstandings about their illness are not uncommon due to a language barrier.<sup>18,19</sup> Evidence suggests that individuals with lower education tend to have lower health literacy,<sup>17,19</sup> which in turn could negatively impact their understanding of information communicated by health professionals.<sup>17,19</sup> Although there are no published studies investigating the association between patients' functional performance and understanding of their cancer, it seems reasonable that worsening of daily functioning associated with cancer progression could be associated with decreased concentration and ability to process information.

The primary aim of this study was to investigate whether CUP patients with poorer understanding of their cancer diagnosis experience more symptoms of psychological distress, and if this relationship is mediated by their uncertainty about their illness. Our conceptualisation of patients' understanding of their cancer encompasses their retrospective appraisals of how well they understood their diagnosis, their diagnostic testing results, and the reasons for having diagnostic testing. We expected that poorer understanding would predict higher levels of illness uncertainty which would in turn predict higher levels of psychological distress (Figure 1). Given the relevance to both uncertainty in illness and psychological distress symptoms,<sup>20-22</sup> physical symptoms experienced by cancer patients such as fatigue, pain and sleep disturbance were incorporated into the model. We postulated that more physical symptoms would predict higher levels of uncertainty and psychological distress.

The secondary aim of the study was to explore whether CUP patients' understanding of their cancer diagnosis could be predicted by clinical and socio-demographic factors. We investigated if CUP patients who had lower Eastern Cooperative Oncology Group (ECOG) functional performance status, who were older, who were less educated and who were from non-English speaking backgrounds would have poorer understanding of their CUP diagnosis.

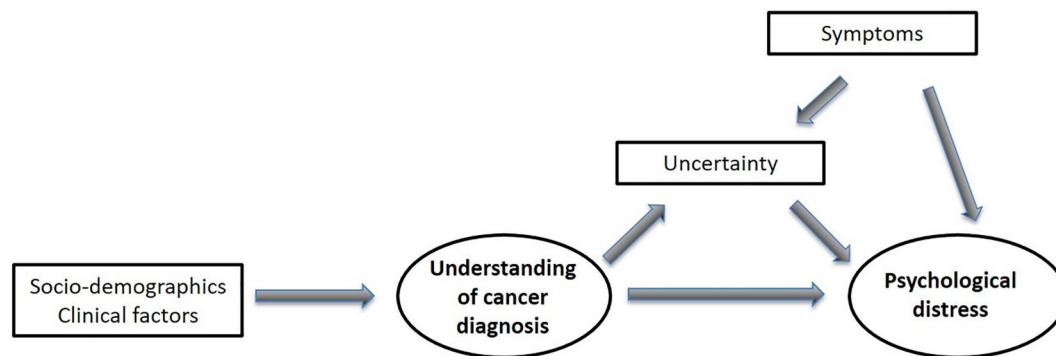


FIGURE 1 The proposed theoretical model

## 2 | METHOD

### 2.1 | Design and setting

This paper presents baseline data from a longitudinal cohort study, Solving Unknown Primary CancER (SUPER), which was conducted nationally across 12 health services and coordinated at Peter MacCallum Cancer Centre in Melbourne, Australia. Solving Unknown Primary CancER is a national collaborative cohort study aiming to: (a) improve the diagnostic assessment of CUP patients; (b) integrate new diagnostic approaches, specifically, molecular therapeutics and treatments for likely site-of-origin; and (c) study the psychosocial needs of CUP patients. The study was approved by the Human Research Ethics Committee of Peter MacCallum Cancer Centre (project number 13/128 and 13/62).

### 2.2 | Participants

Participants were CUP patients who were recruited between November 2013 and November 2018 for the SUPER study. The following inclusion criteria were used in the study: (1) confirmed CUP diagnosis; (2) yet to commence treatment or have commenced treatment no more than 6 months ago; (3) able to read and write in English; and (4) provided written informed consent. Patients who: (1) are under 18 years; (2) have a poor ECOG health performance status (greater than or equal to 3); or (3) have uncontrolled medical or psychological conditions that may prevent completion of study requirements, were excluded from the study.

### 2.3 | Procedure

Treating clinicians presented the study to eligible patients and referred those interested in participating to the study coordinator or study coordinator/research assistant to recruit the patient, after eligibility was confirmed by the treating clinician and consent to participate was obtained. Consenting patients completed a baseline questionnaire. Participants had two options to complete the

questionnaire: (1) completing a mailed-out questionnaire booklet; (2) completing the questionnaire via telephone interview with a trained research assistant who entered the data online.

### 2.4 | Measures

#### 2.4.1 | Sociodemographic

Background characteristics included gender, age, marital status, current employment, level of education, and English as a first language.

#### 2.4.2 | Clinical measures

##### *Eastern Cooperative Oncology Group performance status*

Eastern Cooperative Oncology Group is a commonly used measure of functional status of patients with serious chronic illnesses including cancer, and it helps oncologists assess the impact of cancer on patients' everyday activities and functional status, as well as patients' potential tolerance of aggressive chemotherapy.<sup>23</sup> Higher ECOG scores are indicative of decreased functioning of cancer patients.<sup>23</sup>

#### 2.4.3 | Patient reported questionnaires

##### *Psychological distress*

The Patient-Reported Outcomes Measurement Information System (PROMIS<sup>®</sup>) short forms were employed to assess anxiety and depression. These short forms have been specifically developed and evaluated for use in clinical oncology research and were shown to have high internal consistency and reliability hence represent standardised, accurate and efficient self-report measures.<sup>24</sup>

##### *Physical symptoms*

PROMIS<sup>®</sup> short forms assessing fatigue, sleep disturbance and pain interference were used. These measures have been previously psychometrically evaluated for use in clinical oncology research.<sup>24</sup>

### Uncertainty in illness

The 23-item Mishel Uncertainty in Illness Scale - Community (MUIS-C) Form has demonstrated moderate to high internal consistency ( $\alpha = 0.74\text{--}0.92$ ) and has been widely used in the research focussing on patients with chronic conditions including cancer.<sup>25,26</sup> MUIS-C employs a 5-point Likert-type scale where 1 = *strongly disagree* and 5 = *strongly agree*; the responses are added together to create a total score where low total scores indicate low uncertainty. MUIS measures ambiguity, complexity, inconsistency and unpredictability with regards to clinical issues such as symptomatology, diagnosis, treatment, and patient's planning for the future.<sup>26</sup>

### Patients' understanding of their cancer

Patients' understanding of their cancer was measured using their retrospective appraisals of how well they understood their diagnosis during clinical consultation, and how well they understood their diagnostic testing results and the reasons for having diagnostic testing. These items were derived from UK National Cancer Patient Experience Survey 2011/2012.<sup>27</sup> Patients were asked the following questions: (1) Did you understand the explanation of what is wrong with you? Answered: 1-Yes, *completely*; 2 - Yes, *I understood some of it*; 3 - No, *I didn't understand it*; 4 - *Can't remember*. (2) Were the results explained in the way you could understand? Answered: 1-Yes, *completely*; 2-Yes, *to some extent*; 3-No, *but I would have liked the explanation*; 4-*I didn't need the explanation*; 5-*Don't know/can't remember*. (3) How well did you understand the reasons for having the tests that you have had? Answered: 1- *Very Well*; 2- *Well*; 3- *Not so well*; 4- *Not well at all*.

## 2.5 | Statistical analysis

SPSS Version 28 was used to calculate descriptive statistics for the sample and Pearson's correlations between the variables. Analysis of Moment Structures 26 was employed to conduct SEM to test the proposed theoretical model. There were three latent constructs in this model: (1) psychological distress, which comprised anxiety and depression symptoms; (2) understanding of CUP, which comprised patients' understanding of their cancer diagnosis, understanding of their diagnostic testing results, and understanding of the reasons for having diagnostic testing; and (3) physical symptoms, which comprised pain, fatigue, and sleep disturbance. The paths between understanding of CUP, illness uncertainty, physical symptoms and psychological distress are represented as the structural model (Figure 2). Maximum likelihood estimation was used to fit the model. Model fit was evaluated with a set of goodness of fit indices, including the chi-square, the comparative fit index (CFI), the goodness of fit index (GFI), standardized root mean squared residual (SRMR), Tucker-Lewis index (TLI) and root mean square error of approximation (RMSEA).<sup>28-30</sup> Bias corrected bootstrapping with 2000 samples was used to assess the indirect effect of understanding on psychological distress via uncertainty.

## 3 | RESULTS

The response rate was high: 92% of CUP patients who were approached consented to participate in the study. Demographic and clinical information for the 209 participants is summarised in Table 1. The mean age was 61.6 years, and 53.1% were female. A majority of participants were of English-speaking background and had a good ECOG status (0-1). Nearly 30% of participants had a tertiary education.

The correlations between study variables are depicted in Table 2. Patients' understanding of their cancer was negatively associated with symptoms of depression and anxiety, as well as illness uncertainty. Anxiety and depression were positively correlated with illness uncertainty. Symptoms of cancer such as pain, fatigue and sleep disturbance were positively associated with anxiety and depression. Pain and fatigue were positively correlated with illness uncertainty. Older age was negatively correlated with anxiety and depression and positively associated with patient's understanding of their cancer diagnosis.

### 3.1 | Structural equation model

Understanding of their cancer, illness uncertainty, symptoms, age as well as anxiety and depression as outcome variables were entered into the proposed model. Values for the measurement model were all significant at  $p < 0.01$  and most were over 0.50 indicating good internal consistency amongst indicators of the latent variables.

Model fit was assessed using several criteria. The chi-square indicates the overall fit between the predicted model and observed data.<sup>28-30</sup> In addition, the fit of the model was assessed using the relative chi-square, the RMSEA and 90% confidence interval, the CFI, the Tucker-Lewis Fit Index (TLI), and the standard root mean square residual (SRMR).<sup>28-30</sup> The criteria for assessing 'good' and 'acceptable' model fit for these fit indices are indicated in Table 3. A significant chi-square ( $P < 0.05$ ) suggests poor fit.<sup>28-30</sup> The criterion for relative chi-square is  $< 2$  for good fit and  $< 3$  for acceptable fit.<sup>28-30</sup> RMSEA and SRMR values  $< 0.05$  indicate good fit, and values  $> 0.10$  indicate poor fit.<sup>28-30</sup> For both the CFI and the TLI, a value of one indicates perfect fit, while values  $> 0.95$  and  $> 0.90$  indicate good fit and acceptable fit, respectively.<sup>28-30</sup>

The initial model did not have a good fit. The chi-square indicated a significant deviation of the predicted model and observed data ( $\chi^2 = 305.244$ ,  $df = 148$ ,  $p < 0.001$ ), the relative chi-square was above 2 and the goodness of fit indices were below the acceptable thresholds (CFI = 0.88, GFI = 0.89, TLI = 0.88). The clinical factors such as ECOG status and time since diagnosis as well as socio-demographic factors including education and English as first language were removed from the model as they did not have significant associations with patient's understanding of their cancer diagnosis, or anxiety and depression. After making these changes, the final model (Figure 2) showed a good fit as reported in Table 3.

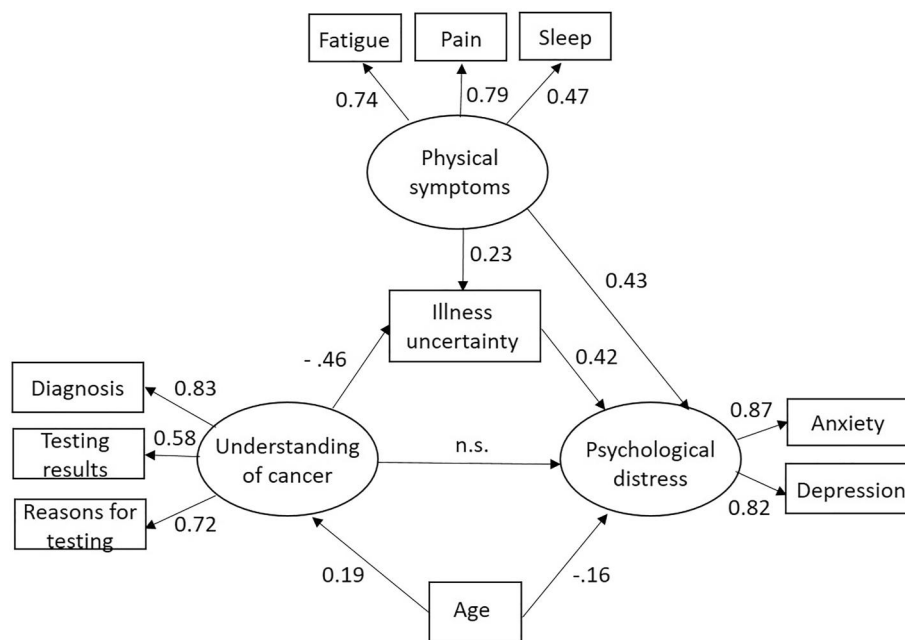


FIGURE 2 The structural equation model. Standardized coefficient values are depicted in the model

TABLE 1 Demographic and clinical characteristic of Cancer of Unknown Primary (CUP) patients in the sample

| Variable  | N (%) or M (SD)<br>(n = 209) |
|---|------------------------------|
| Sex   |                              |
| Males   | 98 (46.9)                    |
| Females   | 111 (53.1)                   |
| Age in years, M (SD)                                  | 61.6 (12.6)                  |
| ECOG status   |                              |
| 0   | 65 (31.1)                    |
| 1   | 116 (55.5)                   |
| 2   | 28 (13.4)                    |
| Time from cancer diagnosis to consent in days, M (SD) | 54 (75.8)                    |
| Higher level of formal education                      |                              |
| No formal schooling, primary, secondary               | 103 (50.2)                   |
| Tertiary  | 61 (29.8)                    |
| Trade, TAFE, college                                  | 41 (20.0)                    |
| English As first language                             | 186 (87.6)                   |

The model showed that lower understanding predicted higher illness uncertainty and, in turn, higher illness uncertainty predicted higher psychological distress. More physical symptoms predicted higher illness uncertainty and higher psychological distress, whereas younger age was associated with lower understanding of cancer and higher psychological distress. There was no direct relationship between understanding and psychological distress, instead the

relationship between understanding and psychological distress was fully mediated by illness uncertainty. The significance of indirect effect of patient's understanding of their cancer on psychological distress via illness uncertainty was conducted using Bootstrap analysis ( $-0.193$ , 95CI:  $-0.298, -0.107$ ,  $p = 0.001$ ).

## 4 | DISCUSSION

The SEM results revealed that CUP patient's understanding of their cancer predicts psychological distress and that this effect is mediated by illness uncertainty. This finding is in agreement with previous studies that identified positive association between uncertainty and psychological distress in various cancer types.<sup>9-12</sup> The implications of illness uncertainty in the context of CUP are particularly important since these patients face a challenging situation regarding the unknown origin of their cancer, frequently a dismal prognosis, and limited treatment options.<sup>1,2</sup> In recent years there have been significant improvements in histopathological analysis and imaging methods as well as genomic testing which can help identify likely site of cancer origin and reveal actionable gene mutations that can be targeted with selective anti-cancer therapeutic drugs.<sup>31,32</sup> The advancements in these analyses might not only improve the treatment options for CUP patients but also improve their understanding of their cancer, reduce their uncertainty, and consequently improve their mental wellbeing. Providing CUP patients with adequate written information about their diagnosis and test results tailored to their individual needs may improve their understanding of their cancer as suggested by Wagland and colleagues.<sup>15</sup> In line with our findings, ensuring that CUP patients have good understanding of their illness would result in more

TABLE 2 Pearson correlations between study variables

| Variable                     | 1       | 2      | 3     | 4      | 5     | 6      | 7      | 8      | 9      | 10      | 11     | 12     | 13 |
|------------------------------|---------|--------|-------|--------|-------|--------|--------|--------|--------|---------|--------|--------|----|
| 1. Age                       | -       |        |       |        |       |        |        |        |        |         |        |        |    |
| 2. Gender                    | -0.18*  | -      |       |        |       |        |        |        |        |         |        |        |    |
| 3. Level of education        | -0.26** | -0.14  | -     |        |       |        |        |        |        |         |        |        |    |
| 4. English as first language | 0.14*   | -0.15* | 0.15* | -      |       |        |        |        |        |         |        |        |    |
| 5. Time since diagnosis      | 0.00    | -0.02  | -0.08 | -0.15* | -     |        |        |        |        |         |        |        |    |
| 6. ECOG                      | 0.09    | -0.04  | -0.06 | -0.06  | -0.10 | -      |        |        |        |         |        |        |    |
| 7. Fatigue                   | 0.00    | 0.09   | -0.11 | -0.03  | 0.02  | 0.26** | -      |        |        |         |        |        |    |
| 8. Pain                      | 0.01    | 0.00   | -0.08 | -0.02  | -0.12 | 0.25** | 0.62** | -      |        |         |        |        |    |
| 9. Sleep disturbance         | -0.06   | 0.02   | -0.00 | 0.12   | -0.05 | 0.08   | 0.31** | 0.36** | -      |         |        |        |    |
| 10. Understanding of cancer  | 0.16*   | -0.09  | 0.03  | 0.06   | -0.04 | -0.04  | -0.11  | -0.06  | -0.01  | -       |        |        |    |
| 11. Illness uncertainty      | -0.08   | 0.15*  | -0.11 | -0.08  | 0.04  | 0.05   | 0.21** | 0.23** | 0.07   | -0.44** | -      |        |    |
| 12. Anxiety                  | -0.17   | 0.17*  | -0.06 | 0.01   | -0.02 | -0.03  | 0.32** | 0.34** | 0.31** | -0.21** | 0.49** | -      |    |
| 13. Depression               | -0.18** | 0.16*  | -0.08 | 0.01   | 0.05  | -0.01  | 0.38** | 0.35** | 0.30** | -0.23** | 0.42** | 0.72** | -  |

Note: ECOG = Eastern Cooperative Oncology Group measure of functionality.

\* $p \leq 0.05$ ; \*\* $p \leq 0.01$ .

TABLE 3 Criteria for the Goodness of fit indices and the corresponding values for the final model

| Goodness of fit index | Criteria for fit |             | Observed value     | Goodness of fit assessment |
|-----------------------|------------------|-------------|--------------------|----------------------------|
|                       | Good             | Acceptable  |                    |                            |
| $\chi^2/df$           | $\leq 2$         | $\leq 3$    | 1.48               | Good                       |
| SRMR                  | $\leq 0.05$      | $\leq 0.10$ | 0.053              | Acceptable                 |
| CFI                   | $\geq 0.97$      | $\geq 0.95$ | 0.975              | Good                       |
| TLI                   | $\geq 0.95$      | $\geq 0.90$ | 0.963              | Good                       |
| RMSEA [90% CI]        | $\leq 0.05$      | $\leq 0.08$ | 0.048 [0.01-0.076] | Good                       |

Abbreviations: CFI, comparative fit index; CI, confidence interval; *df*, degree of freedom; RMSEA, root mean square or approximation; SRMR, standardized root mean square residual; TLI, Tucker-Lewis index.

certainty around some aspects of their cancer, thus potentially contributing to better psychological functioning.

Interestingly, neither clinical nor sociodemographic factors except for age were associated with patient's understanding of their cancer. Our assumption that older age would predict poorer understanding of cancer diagnosis was not supported by our findings. By contrast, younger patients tended to have a poorer understanding of their cancer. A potential explanation could be that younger people have higher needs regarding understanding of their cancer and the information provided to them by their clinician could be perceived as inadequate or insufficient.<sup>33</sup> Another interpretation could be that younger patients are more susceptible to the negative impact of the shock surrounding cancer diagnosis and hence experience more difficulties with psychological adjustment, which can impair their cognitive capacities.<sup>34-36</sup>

Performance status as measured by ECOG status was not associated with level of understanding of illness by CUP patients: discordant with our assumption. However, over 80% patients in our

study had a good performance status as this was an eligibility requirement, which is a limitation of our data set. We found level of education did not predict CUP patients' comprehension of their cancer. Richardson et al (2015) demonstrated that CUP patients struggle with comprehending the fact that clinicians may not be able to identify the source of their primary tumour.<sup>5</sup> It could be speculated that in our sample a higher level of education did not reflect an adequate health literacy that would enable patients making sense of the ambiguity and complexity surrounding CUP diagnosis. In contrast to previous studies in various cancer types, CUP patients for whom English was not first language showed no difference in the understanding of their illness than native English speakers. One likely explanation is that sufficient English was used as one of the eligibility criteria in our study. Furthermore, it is possible that CUP patients from non-English speaking backgrounds attended their appointments accompanied by their family members or friends who had sufficient English competency and were able to assist them with the understanding of the medical information provided by the clinician.<sup>37</sup>

## 4.1 | Study limitations

The major limitation of this study is the cross-sectional nature of the design which does not allow for investigation of causation between the variables. The study was conducted only in Australian hospitals and only good performance status patients were eligible for the study, hence the generalizability of our findings could be limited. Additionally, our study relied on self-report measures for assessment of anxiety and depression, and more importantly patients with severe psychological distress were excluded from our study. For these reasons the interpretation of the results should be taken with caution and further studies are needed to replicate our findings.

## 4.2 | Clinical implications

Consistent with previous studies investigating psychological distress in other cancer types,<sup>20-22,34,35</sup> our findings identified, younger age, and physical symptoms such as fatigue, pain and sleep disturbance as key predictors of higher levels of psychological distress in CUP patients. This information could be clinically relevant and used to identify most vulnerable individuals who might benefit from psychological support and extra level of care. Importantly, we found that illness uncertainty mediates the relationship between poor understanding of cancer and higher psychological distress and that younger individuals are more likely to find understanding of their cancer challenging. This finding is clinically actionable and modifiable since patients' understanding can be targeted for improvement. Importantly, clinicians should follow communication skills guidelines, which emphasise asking the patients what questions they have and providing them with as much information as they require.<sup>38</sup> This has been shown to be associated with lower levels of psychological morbidity.<sup>38</sup> Patient's understanding about their cancer could be improved by providing tailored information resources, particularly for younger CUP patients who have higher psychological distress. Other approaches could focus on ensuring that clinicians are well educated on CUP patients' information needs, as well creating supervised support groups for CUP patients that could help with information exchange.

Further research is needed to develop resources that could be used to aid clinicians with information exchange, especially for young CUP patients. Our findings highlight an urgent need to improve the quality of communication between healthcare professionals and CUP patients, echoing calls of earlier studies.<sup>3,5</sup> Previous research has made a parallel between CUP and rare cancers,<sup>39,40</sup> and it would be interesting to investigate if our model incorporating patient understanding and illness uncertainty could be applied to other patients with rare illnesses who experience significant psychological distress. It would be also interesting to compare levels of understanding, illness uncertainty and psychological distress among CUP patients in less developed countries who have limited access to advanced diagnostic testing such as genomic analysis.

## 5 | CONCLUSIONS

Our study showed that illness uncertainty of CUP patients' mediated the relationship between understanding about their cancer and psychological distress. Physical symptoms such as pain, fatigue and sleep disturbance as well as younger age were positively associated with psychological distress. An effort should be made to improve level of understanding of CUP patients, as it could enhance their mental wellbeing by reducing uncertainty about their illness. It will be important to conduct further studies to elucidate reasons behind low understanding of their illness by CUP patients.

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### CONFLICT OF INTEREST

All authors of this article declare they have no conflicts of interest to report.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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