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Symptoms of prolonged grief and major depressive disorders: Distinctiveness and temporal relationship in the first 2 years of bereavement for family caregivers of terminally ill cancer patients

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Abstract

Objective: Prolonged grief disorder (PGD) and major depressive disorder (MDD) are common syndromes shaping bereaved caregivers' quality of life (QOL). However, distinctiveness of these syndromes warrants confirmation, and the temporal relationship of PGD and MDD symptoms has not been established. To fill these knowledge gaps, we conducted this longitudinal study.

Methods: PGD symptoms, depressive symptoms, and psychological QOL were measured over 398 caregivers' first 2 years of bereavement using the Prolonged Grief-13 (PG-13) scale, Center for Epidemiologic Studies-Depression (CES-D) scale, and Short Form-36 Health Survey mental health summary, respectively. To clarify the distinctiveness of PGD and MDD symptoms, we examined their associations with psychological QOL by incremental validity testing. Distinctiveness and temporal relationship of PGD and MDD symptoms were also examined using longitudinal, lower-level mediation analysis with a lagged approach.

Results: After the variance in psychological QOL was explained by CES-D scores (pseudo-R^2 = 44.19%, P < .001), PG-13 scores significantly, incrementally increased the explained variance in psychological QOL (pseudo-R^2 = 0.21%, P < .001), confirming the distinctiveness of PGD and MDD symptoms. CES-D scores mediated 40.7% of the time vs PG-13 score relationship, whereas PG-13 scores mediated 78.2% of the time vs CES-D score relationship with a better model fit, indicating that PG-13 scores assessed earlier mediated caregivers' current depressive status rather than vice versa.

Conclusions: PGD and MDD are distinct constructs, and PGD precedes onset of MDD. Clinicians should distinguish between these two disorders and address bereaved caregivers' PGD to reduce PGD-associated distress and morbidity and to prevent MDD onset, thereby improving their QOL.

1 | INTRODUCTION

Bereavement is one of life's most stressful events,[1,2] and the most common emotional reaction during bereavement is grief, which tends to resolve over time.[2] However, a strong and persistent grief reaction increases psychological stress for bereaved family members, resulting in prolonged grief disorder (PGD), major depressive disorder (MDD), and poor quality of life (QOL).[3]

PGD and MDD are common mental disorders following bereavement (ie, death of a significant other). Their symptoms are similar yet distinct; both result in distress and QOL impairment,[3,4] despite different etiologies.[5,6] Symptoms of "prolonged grief" stem from attachment issues.[5] During early development, intimate emotional connections with significant others are critical for individuals to feel secure while interacting with the outside world[7]; grief is a reaction to the permanent separation from a loved one. Inability to adjust to the permanent separation from a loved one (ie, death of a loved one) can have psychological consequences, progressing to prolonged grief.[7,8] Depression has the following cognitive characteristics: negative interpretations of information, distortions in thinking about failure or success, and negative perceptions of oneself, the world, and the future, resulting in feelings of hopelessness.[6] These characteristics are recognized as cognitive errors (distortions), negative self-schema, and a cognitive triad of negative thoughts/perceptions.[6]

PGD and MDD are classified by the *Diagnostic and Statistical Manual of Mental Disorders*, version 5 and the *International Classification of Diseases* as two different types of mental disorders.[9,10] Symptoms of PGD and MDD have been found largely by confirmatory factor analysis to be distinct constructs.[11-15] To confirm whether these two conditions are the same or distinct constructs, one can also use incremental validity testing.[16] Incremental validity refers to whether one variable (A) uniquely predicts an outcome variable over and above the variance predicted by a second variable (B), thus ruling out total collinearity between the two constructs and establishing their distinctiveness.[16]

PGD and MDD symptoms for bereaved individuals were examined in a two-part study to evaluate their distinctiveness by incremental validity testing.[17] The first part, a longitudinal study of 73 bereaved people 4 and 18 months after the death of their loved one showed that PGD and MDD symptoms were distinct syndromes. However, PGD cannot be diagnosed until symptoms are sustained longer than 6-month postloss.[3] Therefore, using PGD symptoms measured at 4-month postloss may not be valid. The second part, a cross-sectional study,[17] assessed PGD and MDD symptoms of 447 bereaved people 2.5 to 3.5 years after losing a loved one due to a catastrophe (the USA 9/11 terrorist attacks), thus failing to illustrate the incremental validity of changes in bereaved people's two emotional disorders,[4,18] especially during the first 2 years of bereavement when grief reactions evolve quickly. Furthermore, bereaved participants in that study[17] were not necessarily the decedent's primary caregiver. Grief from unnatural deaths can be more profound and prolonged than grief from the expected death of a beloved after a terminal illness.[19] Therefore, the findings may not be generalizable to primary caregivers of terminally ill cancer patients who experience a heavy caregiving burden[20] and endure negative bereavement outcomes.[21,22]

Distinctiveness of PGD and MDD for bereaved caregivers can also be examined by lower-level mediation analysis. This statistical approach[23] facilitates investigation of changes in predictors and mediators across time (representing level 1 of the analysis), nested within participants (representing level 2 of the analysis). Lower-level mediation analysis differs from upper-level mediation analysis, which aims to investigate between-group differences (eg, in gender or age).[23] If PGD and MDD are expressions of the same latent concept, these constructs will have a bidirectional relationship, in which change in each construct will predict about the same change in the other construct's variance.[24] In contrast, if the two constructs are different, lower-level mediation analysis will reveal that changes in each construct predict a considerably different amount of change in the variance of the other construct.[23-25]

PGD and MDD as well as their symptoms may coexist after bereavement. For example, bereaved individuals with MDD had higher rates of PGD.[26] Furthermore, caregivers with PGD symptoms also have significant depressive symptoms.[13] However, no studies have explicitly explored the temporal relationship of these two constructs, despite such a relationship being established for symptoms of PGD and posttraumatic stress disorder (PTSD) following bereavement.[24,27] Indeed, PGD symptoms were shown to precipitate PTSD symptoms following bereavement rather than vice versa.[24,27] Information on the temporal relationship between PGD and MDD is important to guide development of effective interventions to avoid the subsequent emotional disorder. The temporal relationship of PGD and MDD during bereavement can be examined by a lagged approach[27] in lower-level mediation analysis[24] (ie, depressive symptoms measured in the previous wave of assessment might mediate current PGD symptoms or vice versa). A lagged approach can directly establish a chronological order,[28] despite reducing statistical power by sacrificing one time point.[29] However, with a sample of at least 200, the loss of statistical power may be neglible.[29]

The aims of this study were to (a) verify whether PGD and MDD are distinct disorders for bereaved caregivers of terminally ill cancer patients by longitudinally examining the incremental association of PGD symptoms and QOL over and above the variance predicted by depressive symptoms and (b) validate the distinctiveness of these two disorders and establish their temporal relationship by a lagged

approach in low-level mediation analysis over caregivers' first 2 years of bereavement. Herein, we use "PGD" and "MDD" when referring to clinical diagnoses and "PGD and depressive symptoms" when referring to outcomes measured by the Prolonged Grief-13 (PG-13) scale[3] and Center for Epidemiologic Studies-Depression (CES-D) scale,[30] respectively.

2 | METHODS

2.1 | Research design and sample

The data for this study came from two longitudinal studies on associations between end-of-life caregiving and family caregivers' depressive symptoms, QOL, and PGD before and after their loved one's death.[4,18] For these studies, caregivers were recruited by convenience from December 2006 to December 2012 and followed until their loved one died (end April 2017). Bereaved caregivers were followed through the first 2 years of bereavement. Caregivers were eligible for the study if they met the following criteria: (a) identified by the patient as the family member most responsible for their daily care; (b) the care recipient's cancer was terminal or advanced, as determined by the patient's oncologist; and (c) 20 years or older and cognitively competent to communicate with data collectors. The Institutional Review Boards of the study sites approved the research protocols (95-1371B and 98-0476B), and each participant provided signed informed consent.

2.2 | Measures

PGD symptoms were measured using only 11 items of the 13-item PG-13,[3] without the two dichotomous items on duration and impairment criteria, which measure other dimensions than grief symptoms, an approach adopted previously.[19,31] Of the PG-13 items, items 1 and 2 measure the frequency of longing/yearning and intense feelings of pain, sorrow, and grief related to the loss of a loved one, respectively, on a 5-point scale (from 1 [*not at all*] to 5 [*several times a day*]). Items 4 and 5 measure the frequency of trying to avoid reminders of the loved one and feeling stunned by the loss, respectively, on a 5-point scale (from 1 [*not at all*] to 5 [*several times a day*]). Items 6 to 12 assess the intensity of current feelings about the loss on a 5-point scale (from 1 [*not at all*] to 5 [*overwhelmingly*]). Total PGD scores (range = 11-55) are calculated by summing the 11 grief-symptom items; higher scores reflect more PGD symptoms.[19,31]

Depressive symptoms were measured with the 20-item CES-D.[30] Depressive symptoms are measured on four subscales: positive emotions, depressive emotions, physical activities, and social difficulties. Items are scored for frequency during the past week using a 4-point Likert scale from 0 (*rarely* [less than 1 day a week]) to 3 (*most or all of the time* [5-7 days a week]). Total scores range from 0 to 60 points; higher scores indicate more depressive symptoms.[30]

QOL was measured with the 36-Item Short Form Survey (SF-36).[32] This self-report instrument assesses physical and mental components of health in eight areas: (a) physical functioning; (b) social role limitations resulting from physical or emotional problems; (c) physical role limitations resulting from health problems; (d) bodily pain; (e) general mental health (psychological distress and well-being); (f) role limitations resulting from emotional problems; (g) vitality (energy and fatigue); and (h) general health perceptions.[32] These areas are considered by the World Health Organization as representing generalized QOL.[33(p1405)] Each scale is directly transformed into a 0 to 100 scale on the assumption that each question carries equal weight; lower scores indicate poorer QOL.[32] The eight areas can be combined into two component scores for physical and mental health, the Physical Component Summary (PCS) and Mental Component Summary (MCS), respectively.[32] Because PGD and depressive symptoms indicate psychological disturbance, the MCS score was used as the dependent variable for psychological QOL (psy-QOL).

2.3 | Data collection

Caregivers were interviewed in person for their baseline preloss caregiving experience (on average 110.00 days [SD: 136.73, median: 62.00, range: 1-912] before patient death) and approximately every 2 to 4 weeks thereafter until they declined to participate. Bereaved caregivers were surveyed 6-, 13-, 18-, and 24-month postloss by phone interviews and mail when necessary.

2.4 | Data analysis

To examine incremental validity, we used PGD and depressive symptoms as predictors and psy-QOL as the dependent variable. Analysis was performed with hierarchical linear modeling (HLM). In the first step, time since bereavement was used as the independent variable, followed by depressive symptoms, and finally, PGD symptoms were added. HLM does not provide true R^2 values; therefore, goodness of fit for the models was determined using pseudo-R^2.[17,34] Significance of the variables in the regression model was set at $P < .05$ for incremental explanatory power.

Longitudinal, lower-level mediation analyses were performed with Mplus 7 software to assess the mediation effect of PGD and depressive symptoms for changes in depressive and PGD symptoms, respectively, over the first 2 years of bereavement. To establish a two-level mediation model, three conditions must be met: (a) the effect of the independent variable relative to the mediation variable is significant; (b) the mediation variable relative to the outcome variable is significant; and (c) after adding the mediation variable, the coefficient for the independent variable on the outcome variable becomes smaller.[23,35] If both models for examining the mediation effects of PGD and depressive symptoms are confirmed, the amounts of variance explained by the two mediation variables (PGD symptoms or depressive symptoms) would indicate the similarity or distinctiveness of the two constructs. If they are the same, their relationship should be bidirectional, indicated by approximately the same amount of

change in variance in one construct being explained by the other construct.[24]

Once the two constructs were shown to be distinct, we used information criteria (ICs) to determine which model better fit the data, ie, which variable had better efficacy as a mediator.[36] Model selection was determined by the Akaike information criterion (AIC) and Bayesian information criterion (BIC),[36] which are penalized likelihood criteria, with a smaller AIC and BIC indicating the better model.[36] Since we adopted a lagged approach to set the chronological order of the two constructs,[28] once the best model for lower-level mediation analysis was set, we could establish the temporal relationship between the distinct constructs of PGD and depressive symptoms.

3 | RESULTS

3.1 | Participants

The case flow of participants from preloss to 24-month postloss is shown in Figure 1. Detailed information has been reported[14] for the numbers of participants who withdrew before and after their loved one's death and reasons for attrition. The numbers of bereaved caregivers who completed postloss surveys (completion rates) were 388 at 6 months (78%), 354 at 13 months (71%), 309 at 18 months (62%), and 292 at 24 months (58%). Comparison of CES-D and PG-13 scores on the four postloss surveys for caregivers who did and did not
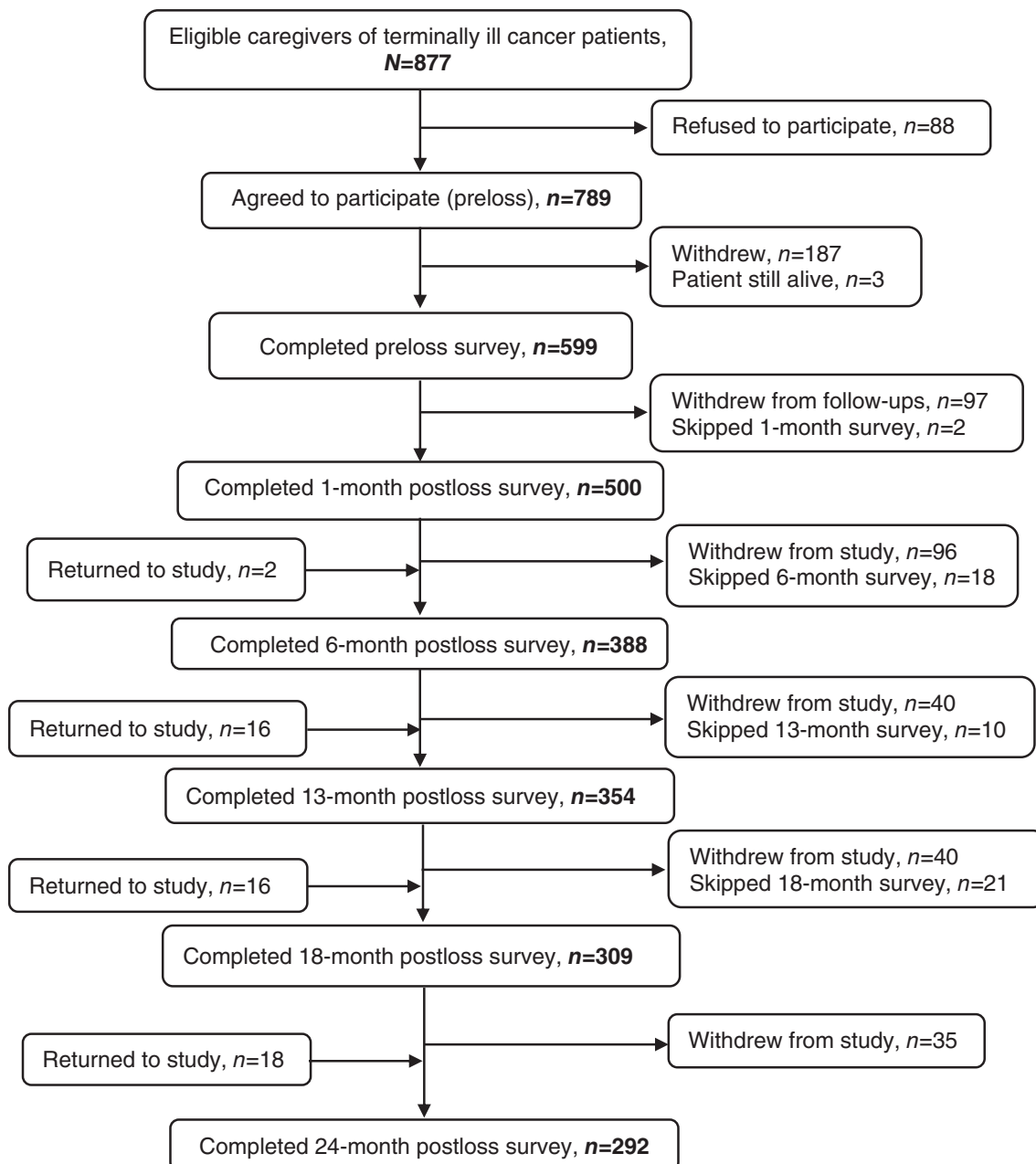
FIGURE 1 Study case flow for participant caregivers of terminally ill patients before and after patient death

withdraw showed no significant differences, except that caregivers who withdrew had significantly more depressive symptoms 13-month postloss than those who participated in the 18-month postloss survey (data not shown). The 398 caregivers who participated in the postloss follow-up surveys were on average 48.33 years old (range: 20-83); most were female (64.1%), and 51.5% were the patient's spouse.[14]

3.2 | Incremental validity testing suggests that PGD and depressive symptoms are distinctive

Incremental validity was first tested for depressive symptoms as a predictor of psy-QOL. Depressive symptoms significantly explained the variance in psy-QOL (pseudo-R^2 = 44.19%, P < .001) (Table 1). When PGD symptoms were added to the HLM model for bereaved caregivers' psy-QOL, PGD scores significantly increased the explained variance over and above (pseudo R^2 = 0.21%, P < 0.001) the variance explained by depressive symptoms.

3.3 | Lower-level mediation analysis confirms the distinctiveness of PGD and depressive symptoms and shows that changes in PGD symptoms precede the changes in depressive symptoms

Our longitudinal, lower-level mediation analyses with lagged variables demonstrate the mediation effects of PGD and depressive symptoms (Figure 2). For the mediation effect of PGD symptoms (Figure 2A), at longer times since bereavement, PGD symptoms were fewer, whereas with more PGD symptoms, depressive symptoms were greater. After adding the mediation variable (PGD symptoms), the coefficient for independent variable (time since bereavement) to the outcome variable (depressive symptoms) decreased significantly from −0.262 to −0.057 (P < .05). Similarly, when a bereaved caregiver's depressive symptoms comprised the mediation variable (Figure 2B), at longer times since bereavement, depressive symptoms were fewer, and with more depressive symptoms, PGD symptoms were greater. After adding the mediation variable (depressive symptoms), the coefficient for the independent variable (time since bereavement) on the

outcome variable (PGD symptoms) decreased significantly from −0.327 to −0.194 (P < .001).

Although these models both demonstrate mediation effects (Table 2), the variances explained were different. If PGD symptoms comprise a mediation variable, 78.2% of the variance in depressive-symptom changes over time is explained, whereas if depressive symptoms comprise a mediation variable, 40.7% of the variance in PGD-symptom changes over time is explained. The amount of variance explained by the two variables differed without a totally bidirectional relationship, confirming that the two constructs are not completely the same.
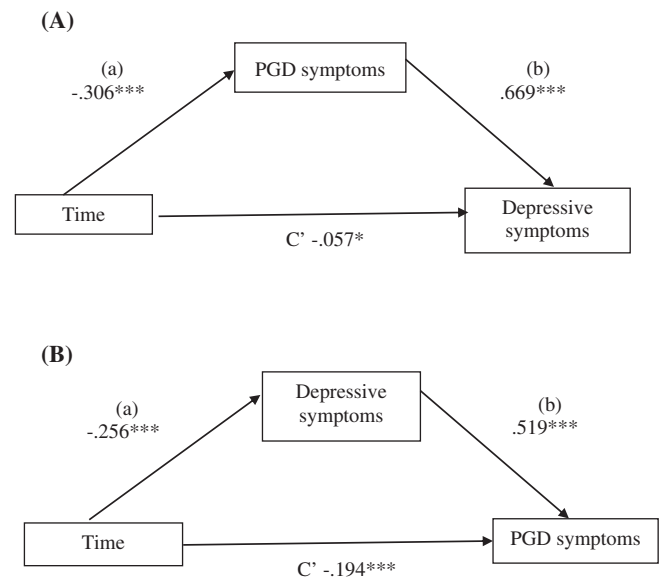
After confirming that the two constructs are distinct, we examined which model better fit the data using the AIC and BIC. IC values for PGD symptoms (AIC: 14 969.33; BIC: 15 015.56) were lower than those for depressive symptoms (AIC: 14 987.10; BIC: 15 033.33), indicating that the mediation effect of PGD symptoms was better than that of depressive symptoms.[35] Therefore, PGD symptoms measured in the prior wave of assessment predicted current depressive symptoms, explaining a greater variance in depressive-symptom changes over the first 2 years of bereavement than the mediation effect of depressive symptoms as a predictor of PGD symptoms following bereavement.

FIGURE 2   Model of the mediating roles played by prolonged grief disorder (PGD) symptoms and depressive symptoms for bereaved caregivers. A, Model showing the mediating role of PGD symptoms and the relationship between time and depressive symptoms. B, Model showing the mediating role of depressive symptoms and the relationship between time and PGD symptoms. a = Direct effect of independent variable (TIME) on mediator (PGD symptoms in A and depressive symptoms in B). b = Direct effect of mediator (PGD symptoms in A and depressive symptoms in B) on outcome variable (depressive symptoms in A and PGD symptoms in B). c′ = Direct effect of independent variable (TIME) on outcome variable (depressive symptoms in A and PGD symptoms in B). *P < .05; ***P < .001

TABLE 1   Analysis of incremental validity for depressive symptoms and PGD symptoms measured with the CES-D and PG-13

Variable	Covariance Estimate	Variation, %	P
Time (as intercept)	27.95		
Increase in CES-D score	15.60	44.19	<.001
Increase in PG-13 score	15.54	0.21	<.001

Note: Variation is the variance explained for psychological quality of life (psy-QOL).
Abbreviations: CES-D, Center for Epidemiologic Studies-Depression; PGD: prolonged grief disorder; PG-13, Prolonged Grief-13.

TABLE 2 Indirect effects of mediators and total effects on the time-outcome relationship

Effect	Mediator/Outcome Variable	
	PG-13/ CES-D	CES-D/ PG-13
Indirect effect (a * b in Figure 2)	−0.205	−0.133
Total effect (c = a * b + c′ in Figure 2)	−0.262	−0.327
Mediating effect	0.782	0.407
AIC	14 969.33	14 987.10
BIC	15 015.56	15 033.33

Abbreviations: Akaike information criterion; BIC, Bayesian information criterion, CES-D, Center for Epidemiologic Studies-Depression; PG-13, Prolonged Grief-13.

4 | DISCUSSION

Our longitudinal study using incremental validity testing and lower-level mediation analyses with a lagged approach not only validated the distinctiveness of the two constructs but also showed that changes in PGD symptoms preceded the changes in depressive symptoms following the loss of a loved one rather than vice versa.

PGD symptoms had a unique, incremental effect, over and above that of depressive symptoms, on caregivers' psy-QOL over their first 2 years of bereavement. Despite the incremental effect in explained variance for psy-QOL being only 0.21% (pseudo-R^2 = 0.21%, $P < .001$), it is still statistically significant,[34] validating the distinctiveness of PGD and MDD. Although our results echo previous longitudinal results,[17] the increased variance explained by PGD symptoms in that study was much higher than ours (2%-7% vs 0.21%). This discrepancy may be related to our PGD prevalence being much lower (1.4%-5.2%) than that in the previous study (10%-17%)[17] because the more dispersed or spread out the outcome variable, the higher the R^2 value.[37]

We used lower-level mediation analysis with a lagged approach to validate the distinctiveness and examine the temporal relationship of PGD and depressive symptoms. When PGD symptoms were the mediator, the model fit was better and changes in PGD symptoms had a considerably stronger impact in the lower-level mediation analyses on subsequent changes in depressive symptoms than vice versa. These results not only verify the distinctiveness of the two constructs but also show the directionality of changes, with changes in PGD symptoms preceding changes in depressive symptoms following the loss of a loved one rather than vice versa. Our finding that PGD symptoms precede the onset of depressive symptoms echoes the observation that PGD symptoms precipitate PTSD symptoms following bereavement rather than vice versa.[24,27]

PGD is triggered by a specific event (bereavement), which is not necessary for depression.[6,8] Losing a significant other results in permanent separation from an important source of emotional support and interpersonal security.[5] Social isolation and feelings of loneliness usually follow the death of loved one, probably due to reluctance to accept outside support and subsequent negative thoughts about oneself, the world, and the future, thereby precipitating development of depression.[6,8] However, people with profound depression tend to maintain fragile interpersonal relationships[38] and losing a family member may not have a strong and prolonged impact on their life, as evident in our findings on the mediating effect of depressive symptoms on changes in PG-13 scores; this effect was substantially less than that of PGD symptoms as a mediator of changes in CES-D scores over the first 2 years of bereavement.

5 | CONCLUSIONS

PGD and MDD are distinct, and changes in PGD symptoms precede the changes in depressive symptoms over the first 2 years of bereavement for caregivers of terminally ill cancer patients.

5.1 | Study limitations

This study had several limitations. First, caregivers of terminally ill cancer patients were a convenience sample from a medical center in northern Taiwan, possibly limiting generalization of our findings to national and international target populations, especially considering the different views of death and grief reactions towards losing a loved one in Western and Asian countries.[4] Bereaved caregivers were assessed for PGD and depressive symptoms with the PG-13 and CES-D scales, respectively, rather than diagnostic interviews by psychiatrists. Using screening questionnaires may overestimate the severity of PGD symptoms and depressive symptoms but avoids missing bereaved caregivers' need for psychological support or treatment. A substantial number of bereaved caregivers withdrew from postloss surveys, limiting the generalization of our findings to those caregivers, despite PG-13 and CES-D scores not differing significantly between those who completed and withdrew from bereavement surveys, except for the 18-month postloss survey. However, these limitations are balanced by the strengths of our study, ie, our longitudinal approach over caregivers' first 2 years of bereavement and our large sample (more than 300) of caregivers who were caring for terminally ill cancer patients. Our longitudinal examination of the incremental validity of the PG-13 and our lower-level mediation analyses with a lagged approach not only verified the distinctiveness of PGD and MDD but also established their temporal relationship.

5.2 | Clinical implications

Health care professionals should recognize PGD and MDD as distinct syndromes, which can incrementally and detrimentally affect bereaved caregivers' QOL. These clinicians should also assess caregivers of end-of-life patients for their PGD risk and use effective strategies to facilitate bereavement adjustment by alleviating PGD not only to reduce its associated distress and morbidity but also to

reduce the subsequent onset of MDD when caregivers finally transit into bereavement. These strategies would avoid substantial intrapersonal,[39] interpersonal,[39] and fiscal burdens[40] for both caregivers and society.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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