

Original Article

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Incidence and risk factors of prolonged grief in relatives of patients with terminal cancer in French palliative care units: The Fami-Life multicenter cohort study

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Abstract

Objectives. Psychological consequences of grief among relatives are insufficiently known. We reported incidence of prolonged grief among relatives of deceased patients with cancer.

Methods. Prospective cohort study of 611 relatives of 531 patients with cancer hospitalized for more than 72 hours and who died in 26 palliative care units was conducted. The primary outcome was prolonged grief in relatives 6 months after patient death, measured with the Inventory Complicated Grief (ICG > 25, range 0–76, a higher score indicates more severe symptoms) score. Secondary outcomes in relatives 6 months after patient death were anxiety and depression symptoms based on Hospital Anxiety and Depression Scale (HADS) score (range 0 [best]–42 [worst]), higher scores indicate more severe symptoms, minimally important difference 2.5. Post-traumatic stress disorder symptoms were defined by an Impact Event Scale-Revised score >22 (range 0–88, a higher score indicates more severe symptoms).

Results. Among 611 included relatives, 608 (99.5%) completed the trial. At 6 months, significant ICG scores were reported by 32.7% relatives (199/608, 95% CI, 29.0–36.4). The median (interquartile range ICG score) was 20.0 (11.5–29.0). The incidence of HADS symptoms was

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87.5% (95% CI, 84.8–90.2%) at Days 3–5 and 68.7% (95% CI, 65.0–72.4) 6 months after patient's death, with a median (interquartile range) difference of -4 (-10 to 0) between these 2 time points. Improvement in HADS anxiety and depression scores were reported by 62.5% (362/579) relatives.

Significance of results. These findings support the importance of screening relatives having risk factors of developing prolonged grief in the palliative unit and 6 months after patient's death.

Introduction

The grieving process has 4 different aspects: anticipatory grief, acute grief, normal grief reactions and complicated grief. The death of a close loved one remains one of the most intense, distressing, and traumatic events a person may experience (Shear *et al.* 2005). Confronted with imminent loss, families experience an emotional burden that includes feelings of helplessness, compassion fatigue, anxiety, and depression, with a strong tendency to stay close to their loved one and provide overprotection. These manifestations are part of the anticipatory grief phenomenon with the anticipation of the future trauma due to loss representation in advance (Coelho and Barbosa 2017). Bereavement can be considered as a continuum from pre-loss to post-loss reactions (Grassi 2007). Bereavement is an existential condition; in some cases, prolonged grief (PG) may occur, the consequences of which may jeopardize quality of life, job conditions, or social relationships, for months, or even years after the loss (Jacobs and Ostfeld 1997). Most of the bereaved individuals are able to get adjusted rather quickly, emotional consequences resolve in few months, and pre-loss functioning is restored after a variable period of 6 to 12 months (Prigerson *et al.* 2009). However, some people may experience prolonged or complicated grief, with emotional, behavioral, and cognitive symptoms (yearning, searching, detachment, numbness, bitterness, emptiness, and loss of sense and control) (Simon 2013). These symptoms may result in a mental illness that is distinct from depression, anxiety, or post-traumatic stress disorders symptoms (Shear *et al.* 2013) and impaired quality of life. PG has been associated with negative outcomes, such as heart disease or changes in eating (Prigerson *et al.* 1997) and suicidal ideation (Prigerson *et al.* 1999).

PG reactions at 8 months were reported in 24.4% (Chiu *et al.* 2010) and at 6 months in 25.4% (Newson *et al.* 2011), 28.6% (Coelho *et al.* 2015), 30% (Wiese *et al.* 2010), and 40% (Guldin *et al.* 2012) of relatives of a heterogeneous population of patients with cancer. Common factors that complicated grief included pre-loss risk factors (female gender, preexisting trauma such as childhood trauma, prior loss, insecure attachment, preexisting mood and anxiety disorders, and nature of the relationships) (Fujisawa *et al.* 2010; Kersting *et al.* 2011; Newson *et al.* 2011), loss-related factors (relationships of caregivers taking roles and nature of the death itself) (Fujisawa *et al.* 2010; Neria *et al.* 2007; Newson *et al.* 2011), and peri-loss factors (social circumstances, resources available after death, poor understanding of the circumstances of death, interference between natural healing process, and culture practices of death) (Bui *et al.* 2013; Hargrave *et al.* 2012; Mutabaruka *et al.* 2012). Although complicated grief decreases over time, its expression varies greatly between individuals, circumstances of death, and culture. Few studies investigated PG reactions in France (Fasse *et al.* 2015); specifically, depression was reported in 25% of spouses of palliative cancer patients between 1 and 6 months after death (Fasse *et al.* 2015).

To bridge this gap, we investigated the incidence and risk factors of PG in a large population of relatives of patients who died in a palliative care unit.

Methods

Study design

This was a prospective multicenter cohort study in 26 French palliative care units. Written informed consent was obtained from both patients and their relatives. Written informed consent was obtained from each relative of patient admitted in the palliative care unit within the first 48 hours of admission. For patients able to make decision, informed consent was obtained directly from the patient, and in other cases, from their surrogate or other relative member if the patient had no surrogate. The trial protocol has been published in Garrouste-Orgeas *et al.* (2019a). The statistical plan is available in Supplement 1.

Setting

Palliative care units from the French Association of Palliative Care (SFAP) were invited to participate in the study by mail. Participating units were required to have ≥ 10 beds and a physician or a nurse or a psychologist who would take responsibility for the study organization and inclusions of relatives and patients. Palliative care units recruited patients from January 2019 to February 2020 (e-Table S1 in Supplement 2). Follow-up was completed in August 2020.

Participants

Inclusion criteria

Consecutive patients with cancer and their relatives admitted in the palliative care unit were approached by physicians or psychologists or nurses. Eligible patients had to be aged at least 18 years to be hospitalized for more than 72 hours for end-of-life issues and to have at least one relative present during the inclusion period and able to visit the patient during the palliative stay. The study was proposed to all relatives present at admission because grief reactions are unique to each relative. The prognostication of end of life was left to the discretion of the physician who examined the patient at admission. Both patients and relatives had to have sufficient French language skills for follow-up telephone interviews. The inclusion period was within 48 hours after palliative care admission.

Exclusion criteria

Patients were ineligible if they had no relatives visiting them during the inclusion period, were under legal guardianship, if their status was considered by the investigator as highly likely to lead to death before 72 hours after admission, if they were not hospitalized for end-of-life issues, and if they had no cancer. Relatives who were mute or deaf or included in another trial with a telephone interview after patient death were also excluded.

Data collection and outcomes

We collected data from centers, patients, and relatives (Supplement 1). Outcomes were measured by 2 psychologists specifically hired for the study (MS and MAL) during telephone interviews conducted 6 months after patient's death. A relative was declared lost to follow-up if he or she could not be contacted by phone after 7 phone calls at different times of the day.

Primary outcome

The primary outcome was the incidence of PG, measured by the Inventory Complicated Grief (ICG) (Zisook et al. 2010a, 2010b) of relatives 6 months after the patient's death in a palliative care unit. Significant PG symptoms were defined by an ICG > 25 (range 0–76, higher scores indicate more severe symptoms). No minimal clinically significant difference was reported for the ICG.

Prespecified secondary outcomes

Anxiety and depression syndrome were evaluated based on the Hospital Anxiety and Depression Scale (HADS) score (Zigmond and Snaith 1983) (range 0 [best]–42 [worst]). Significant anxiety and depression symptoms were defined by a score > 8 for anxiety and depression subscales. The minimal clinically important difference is 2.5 for each subscale (Chan et al. 2016). The evaluation was performed in relatives at Day 3 to Day 5 after patient admission and 6 months after patient's death.

Post-traumatic stress disorder symptoms were evaluated in relatives at 6 months after patient's death, through the Impact Event

Scale-Revised (IES-R) questionnaire (Rash et al. 2008), with significant symptoms defined as an IES-R score > 22 (range 0–88, higher score indicates more severe symptoms) (de Miranda et al. 2011; Garrouste-Orgeas et al. 2019b). There is no minimal clinically significant difference reported for the IES-R score. We reported scores in the 3 domains (intrusion, avoidance, and hyper arousal) that make up the IES-R score.

Statistical analysis

Results are reported as the median and interquartile range (IQR) or as counts (%). Categorical variables were compared using Chi-square test, and continuous variables were compared using Mann-Whitney test.

To assess the risk factor of PG, we used univariate mixed logistic regression with random effects on patients and centers. Centers with less than 10 patients were grouped together. The log linearity of all continuous variables was checked. The non-log linear variables were discretized into categorical variables. Nonlinear and medically logical variables with a $p < 0.1$ were used in a multivariate mixed model with random family and center effect after backward selection.

Anxiety and depression syndrome between Day 3 and Day 5 after patient admission and 6 months after patient's death and post-traumatic stress disorder symptoms 6 month after patient's death were investigated using the same methodology.

The confidence intervals were calculated according to a binomial distribution approximated by a normal distribution. Missing values for univariate and multivariate analyses were considered by a simple imputation method if less than 20% of data were missing. Variables with more than 20% of data missing were not used in the analyses.

The relationship between outcomes and period of COVID-19-related lockdown was tested in the analysis. Analyses were performed using SAS 9.4 (SAS, Inc., Cary, NC) software, and 2-sided $p < 0.05$ was considered statistically significant.

Results

Study population and follow-up

Among the 108 invitations sent out, 17 (15.7%) centers declined participation and 65 (60%) did not answer, leaving 26 (24%) palliative care centers that participated on the study. Recruitment period is reported in e-Table S1 in Supplement 2. Reasons for non-participation were lack of interest in the study ($n = 3$), no time for the study ($n = 3$), and fear of inclusion of relatives close to the patient admission ($n = 11$). Characteristics of the 26 palliative care units are reported in Table 1. Overall, 609 patients and 854 relatives were assessed for eligibility, and 531 patients and 611 relatives were included. Follow-up at 6 months with full completion of the ICG was obtained in 608/611 (99.5%) relatives (Figure 1). Baseline characteristics of patients and eligible, excluded and included relatives are reported, respectively, in e-Tables S2 and S3 in Supplement 2.

Primary outcome

Six months after patient's death, the incidence of relatives with an ICG score greater than 25 was 199/608 (32.7%, 95% CI: 29.0–36.4) (Table 2).

Prespecified secondary outcomes

Within 3 to 5 days after patient admission, symptoms of anxiety (Hospital Anxiety Score [HAS]) were reported by 381 of 583

Table 1. Characteristics of centers

Variables	Data ^a
<i>Hospital</i>	
University hospital, n (%)	7 (23.9)
<i>Palliative care unit</i>	
Number of beds per unit, median (IQR)	12 (10–14)
Number of attending physicians, median (IQR)	2 (1–2.5)
Number of junior physicians, median (IQR)	0 (0–1)
Nurse-to-patient ratio, day, median (IQR)	5 (4–6)
Nurse-to-patient ratio, night, median (IQR)	10 (8–12)
Number of head nurses, median (IQR)	0.8 (0.5–1)
Nursing assistant-to-patient ratio, day, median (IQR)	5 (4–6)
Nursing assistant-to-patient ratio, night, median (IQR)	10 (8–12)
12-hour shifts for nurses (%)	11 (42.3)
12-hour shifts for nursing assistants (%)	11 (42.3)
Number of psychologists, median (IQR)	1 (0.5–1)
Number of physiotherapists, median (IQR)	0.4 (0.2–0.5)
Number music therapist, median (IQR)	0 (0–0)
Number of art therapist, median (IQR)	0 (0–0)
Number socio-aestheticians, median (IQR)	0.1 (0–0.1)
Number of osteopaths, median (IQR)	0 (0–0)
Number of psychomotor therapists, median (IQR)	0 (0–0)
Number of occupational therapists, median (IQR)	0 (0–0)
Number of social workers, median (IQR)	0.3 (0.2–0.5)
Number of hospital biographer (%)	2 (7.2)
Presence of a support group for caregivers, (%)	26 (100)
Presence of a support group for families during the patient stay, (%)	2 (7.7)
Availability of a religious service, (%)	26 (100)
Availability of interpreter services, (%)	21 (80.8)
Availability of volunteers, (%)	26 (100)
Presence of a room with drink dispensers, (%)	17 (64.4)
<i>Visitation policies</i>	
Number of units offering 24-hr visitation, (%)	20 (76.9)
Family on-site sleep	
With a bed into the patient room	25 (96.2)
With an armchair into the patient room	22 (84.2)
Dedicated room available	11 (42.3)
Children visitation authorized, regardless of their age, (%)	26 (100)
Pet visitation authorized, (%)	20 (76.9)
Availability of a mortuary chamber, hours, median (IQR)	8 (7–9)

(Continued)

Table 1. (Continued.)

Variables	Data ^a
<i>Communication with families</i>	
Formal meeting at admission, (%)	26 (100)
With a nurse	24 (92.3)
With a psychologist	13 (50)
Formal weekly meeting, (%)	19 (73.3)
Formal meeting at the patient's death, (%)	14 (53.8)
Delivery of an information leaflet at admission, (%)	26 (100)
Delivery of a leaflet for children, (%)	6 (23.1)
Delivery of an information leaflet at patient' death, (%)	20 (76.9)
<i>Mourning follow-up</i>	
Sending a condolence letter	14 (53.8)
Proposition of a follow-up with a psychologist	18 (78.3)
Proposition of a follow-up with volunteers	1 (4.3)
Presence a support grieving group	7 (26.9)
Another type of follow-up ^b	3 (17.4)

IQR = interquartile range.

^aNo missing data^bAnother follow-up (remembrance ceremony with other grieving family, meeting with a physician, and phone call with a caregiver).

(65.4%) relatives. Symptoms of depression (HAD) were reported by 215 of 583 (36.9%) relatives. The incidence of HADS symptoms was 87.5% (95% CI, 84.8–90.2). The median (IQR) HADS anxiety score was 10 (7–13), and the median (IQR) HADS depression score was 7 (4–10) (Table 2). Six months after patient's death, symptoms of anxiety were reported by 229 of 607 (37.7%) relatives and symptoms of depression by 110 of 607 (18.1%). The incidence of HADS symptoms was 68.7% (95% CI, 65.0–72.4). The median (IQR) HADS anxiety score was 7 (5–10) and the median (IQR) HADS depression score was 4 (2–7). The median (IQR) difference between day 3–5 and 6 months after patient's death was –4 (–10 to 0). Improvement of HADS anxiety and depression scores was reported by 362 of 579 (62.5%) of relatives (Table 2).

The number of patients with an IES-R score greater than 22 was 323/607 (53.2%) with a median (IQR) score of 24 (13–35) (Table 2).

Univariate and multivariate analyses assessing the risk factors of the increase of an ICG score to greater than 25 in relatives are reported, respectively, in e-Table S4 in Supplement 2 and Table 3. The occurrence of respiratory symptoms on admission (OR 1.68, 95% CI, 1.09–2.6, $p = 0.01$), being the patient's spouse (OR 2.85, 95% CI 1.53–5.3, $p = 0.001$), having a support group for relatives in palliative care unit (OR 5.16, 95% CI, 1.65–16.13, $p = 0.005$), and suffering from anxiety (OR 2.26, 95% CI, 1.4–3.67, $p = 0.001$) and depression (OR 1.64, 95% CI, 1.06–2.53, $p = 0.02$) symptoms shortly after patient admission were significantly associated with an ICG score greater than 25.

Univariate and multivariate analyses of post-traumatic stress disorder symptoms are reported, respectively, in e-Table S5 in Supplement 2 and Table 4. Patient's age < 65 years old (OR 2.75, 95% CI, 1.31–5.79, $p = 0.008$) and between 75 and 65 years (OR 1.99, 95% CI, 1.04–3.79, $p = 0.036$), anxiety/psychological suffering of the patient on admission

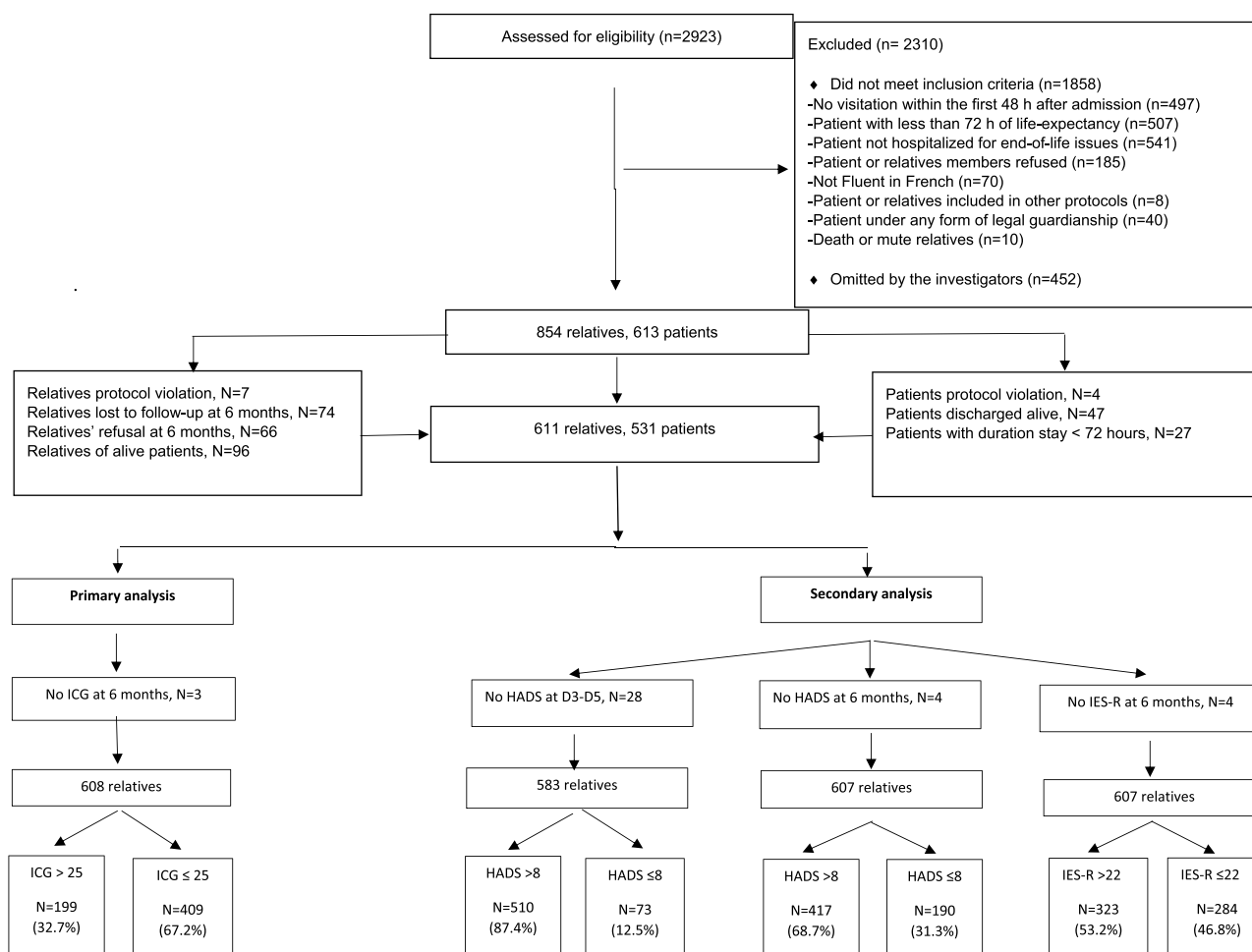


Fig. 1. Flow chart of the study.

(OR 1.63, 95% CI, 1.09–2.42, $p = 0.01$), being a female for the relative (OR 2.75, 95% CI, 1.81–4.17, $p < 0.0001$), being the spouse/partner of the patient (OR 3.48, 95%CI 1.92–6.31 $p < 0.001$), or being the children of the patient (OR 2.05, 95% CI 1.16–3.65, $p = 0.014$) were independent factors of an IES-R > 22.

Univariate and multivariate analyses of anxiety and depression HADS scores between Day 3 and Day 5 after palliative care admission and 6 months after death are reported, respectively, in e-Table S6 in Supplement 2 and Table 5. Presence of patient anxiety/psychological symptoms on admission (OR 1.59, 95 CI 1.04–2.06, $p = 0.01$) was the only factor independently associated with improvement of HADS symptoms in relatives 6 months after patient’s death.

No significant associations were found in the univariate analyses between period of lockdown for COVID-19 in France or not and the different outcomes.

Discussion

This observational multicenter study of the psychological status of relatives 6 months after the death of their loved one in a palliative care unit reported high distress with PG reactions, mainly among spouses and partners. PG reactions were present in one relative out of three, and post-traumatic stress disorder symptoms in one out of two. Patient’s respiratory symptoms at admission and high

psychological distress shortly after patient’s admission were significantly associated with PG. Palliative care admission was associated with high incidence of HADS symptoms with an improvement in 62% of them between 3 and 5 days after patient’s admission and 6 months following death.

This study was performed in palliative care units trained in multidisciplinary care with physical, social, psychological, cultural, and spiritual support of patients, in order to provide relief of pain and physical symptoms. Relatives were included in this multisystemic approach by being offered on-site psychological support, possibility of being close to the patient and being assured that relief was being provided to their loved one. This global approach aimed at providing support and help to relatives for this intense, emotional experience.

Our study found that PG reactions were frequent, present in one-third of relatives. This was consistent with the proportion of 37% of PG reaction (Prigerson et al. 2009). It is important to note than among our relatives, 61.5% were primary caregivers, and this may have overburdened their post-loss experience (Geng et al. 2018; Ghesquiere et al. 2011; Grosse et al. 2018). Pre-loss symptoms or attachment issues are crucial in creating a vulnerable status for developing PG reactions. Being the spouse or partner of the patient was an independent risk factor for PG, in line with other studies (Thomas et al. 2014; van Doorn et al. 1998). Poor adjustment of spouse/partner to grief derived from elements prior to patient’s

Table 2. Primary and secondary outcomes among relatives at 6-month follow-up after patient's death in a palliative care unit

Variables	
Primary outcomes	(N = 608)
Presence of prolonged grief ^f , % (ICG > 25)	199 (32.7)
ICG score, median (IQR)	20 (12–29)
Secondary outcomes	
Anxiety and depression ^b	
At Day 3 to Day 5	(N = 583)
HADS score, median (IQR)	17 (12–23)
HAS score, median (IQR)	10 (7–13)
HAD score, median (IQR)	7 (4–10)
Symptoms of anxiety, %	
Yes	381 (65.4)
Symptoms of depression, %	
Yes	215 (36.9)
At 6-month follow-up	(N = 607)
HADS score, median (IQR)	12 (8–17)
HAS score, median (IQR)	7 (5–10)
HAD score, median (IQR)	4 (2–7)
Symptoms of anxiety, % (HAS score > 8)	
Yes	229 (37.7)
Symptoms of depression, % (HAD score > 8)	
Yes	110 (18.1)
PTSD ^c at 6-month follow-up	(N = 607)
Presence of PTSD symptoms, % (IES-R > 22)	323 (53.2)
IES-R score, median (IQR)	24 (13–35)
Intrusion score	13 (8–9)
Avoidance, score	6 (2–11)
Hyperarousal, score	3 (0–7)

ICG = Inventory Complicated Grief; IQR = interquartile range; HADS = Hospital Anxiety Depression Scale, HAS = Hospital Anxiety Score, HAD = Hospital Depression Score; PTSD = post-traumatic stress disorder.

^aMeasured using the ICG score (range 0–76, higher scores indicates more severe symptoms).

^bMeasured using the HADS score (overall range, 0–42; range for anxiety and depression subscales, 0–21; a higher score indicates more severe symptoms).

^cMeasured using the IES-R score (overall range, 0–88; intrusion range: 0–32; avoidance range: 0–28; hyperarousal range: 0–24; a higher score indicates more severe symptoms).

death (Fasse et al. 2014): presence of cognitive and emotional features, caregiving experience (Marwit et al. 2008), symptoms of the patient's disease (Morita et al. 2007), patient's care and treatments and post-loss factors (perception of cancer in the social network) (Fasse et al. 2014). Low level of active coping in a sample of spouse/partner was the only significant factor associated of developing PG reactions (Miller et al. 2020). Higher levels of inflammatory response were found in the bereaved spouse with severe grief reactions (Fagundes et al. 2019).

Factors of PG were usually explored through the individual relative point of view. Our study added the evaluation of patients and center characteristics. We found that respiratory symptoms in patients at admission were independent factors for PG. Respiratory

Table 3. Multivariable analysis of the occurrence of prolonged grief in relatives of patients who died in a palliative care unit

Variables	OR (95% CI)	p-value
<i>Center</i>		
Formal meeting after patient's death	1.53 (0.89–2.64)	0.11
Presence of a support group for relatives during the stay	5.16 (1.65–16.13)	0.005
Relatives authorized to prepare the body for funerals ^a	0.43 (0.19–0.97)	0.043
<i>Patients</i>		
Age	0.97 (0.95–0.99)	<0.0001
Respiratory symptoms on admission	1.68 (1.09–2.6)	0.0119
Digestive symptoms on admission	0.68 (0.41–1.15)	0.152
<i>Relatives</i>		
Lockdown period ^b	0.66 (0.4–1.1)	0.11
Relationship with the patient		0.001
Spouse/partner	2.85 (1.53–5.3)	0.001
Children	1.64 (0.88–3.04)	0.12
Parents	2.38 (0.555–10.25)	0.24
Other	1	
Presence of anxiety symptoms at Day 3 to 5 after admission	2.26 (1.4–3.67)	0.001
Presence of depression symptoms at Day 3 to 5 after admission	1.64 (1.06–2.53)	0.026

CI = confidence interval; OR = odds ratio.

Variables included in the multivariable analysis: Center's related variables: beds > 15 in palliative care unit, 24 hours visitation policies, family on-site sleep with a dedicated room, authorization for relatives to prepare the body for funerals, organization of an interview with relatives at patient's death, existence of a support group for relatives during palliative care stay; variables related to patient's symptoms: age; symptoms of admission: (anxiety/psychological suffering, sepsis, pain, neurologic, and digestif); relatives' related variables: gender, primary caregiver, relation with the patient, lockdown period in France, presence of anxiety symptoms or presence of depression symptoms between Day 3 and Day 5 after patient admission, on the basis of a p-value <0.1.

^aThe body preparation for funerals is done by the relatives immediately after death with nurses and nursing assistants (washing and dressing the body for funerals and having the possibility to practice religious rite).

^bLockdown period due to Covid-19 pandemic (in France, from 17 March 2020 to 7 June 2020).

symptoms can be traumatizing for relatives with fear that the patient may experience a painful death. Ruminating memories of this period can elicit difficulties of coping (Coelho and Barbosa 2017). Pre-loss anxiety or depression symptoms were independent factors of PG, in line with other studies (Ghesquiere et al. 2013; Lobb et al. 2010; Nielsen et al. 2017; Tsai et al. 2016). Interestingly, our population of relatives of cancer patients suffered anxiety and depression symptoms at the same prevalence than relatives of intensive care patients measured at similar time points after admission (Pochard et al. 2005). Admission in palliative care for some relatives might be a violent phenomenon and might be a witness of unpreparedness to the upcoming patient's death. Screening for emotional distress after palliative care admission could identify relatives at risk of PG reactions and offer them effective interventions starting while the patient is still alive, which may improve their dying experience and facilitate preparedness for the patient's forthcoming death. However, in contrast with small qualitative

Table 4. Multivariable analysis of the occurrence of post-traumatic stress in relatives of patients died in a palliative care unit

Variables	OR (95% CI)	p-value
<i>Center</i>		
Family on-site sleep in a dedicated room	0.67 (0.45–1)	0.05
Relatives authorized to prepare the body for funerals ^a	0.71 (0.34–1.47)	0.35
<i>Patients</i>		
Age, years		0.065
<65	2.75 (1.31–5.79)	0.008
75 < 65	1.99 (1.04–3.79)	0.036
85 < 75	1.67 (0.9–3.11)	0.10
≥85	1	
Digestive symptoms on admission	0.66 (0.42–1.04)	0.08
Anxiety/psychology suffering on admission	1.63 (1.09–2.42)	0.01
Patient's surrogate	1.42 (0.94–2.15)	0.09
<i>Relatives</i>		
Gender		
Female	2.75 (1.81–4.17)	<.0001
Relationship with the patient		0.007
Spouse/partner	3.48 (1.92–6.31)	<.0001
Children	2.05 (1.16–3.65)	0.014
Parents	2.34 (0.59–9.32)	0.22
Other	1	
Age, years		0.123
<45	1.6 (0.78–3.31)	0.20
55 < 45	0.82 (0.42–1.58)	0.548
65 < 55	1.35 (0.78–2.33)	0.288
≥65	1	

CI = confidence interval; OR = Odds ratio.

^aThe body preparation for funerals is done by the relatives immediately after death with nurses and nursing assistants (washing and dressing the body for funerals and having the possibility to practice religious rite).

Variables in the multivariable analysis on the basis of a *p*-value < 0.1 included the following: Center variables: beds > 15 in palliative care unit, 24 hours visitation policies, delivery of a children leaflet, sending a condolence letter, presence of a support group for relatives, possibility of sleeping on site, authorization for relatives to prepare the body for funerals, presence of a mourning follow-up, organization of an interview after patient's death, delivery of an information leaflet at patient's death. Patients' variables (age), symptoms of admission (pain, respiratory, digestive, psychological suffering), cardiac comorbidity, diagnosis of the type of cancer, single patient, presence of advanced directives, designation of a surrogate, and patient's death after continuous deep sedation. Relatives' variables: gender, age, relation with the patient, primary caregiver, level of education equal or superior to bachelor, presence of anxiety symptoms between Days 3 and 5 after admission diagnosed by a HAS score >8, presence of depression symptoms diagnosed by a HAD score >8 between Days 3 and 5 after admission.

studies (Harding et al. 2002; Henriksson et al. 2011; Milberg et al. 2005), our study found that the support group for relatives during palliative care stay provided by some palliative centers was not an effective option as it increased the risk of PG. Actually, relatives may prefer a face-to-face interview with a psychologist instead of sharing their difficulties with other relatives. Differences in study methodology (qualitative vs. quantitative approach) and

Table 5. Multivariable analysis of improvement of HADS score in relatives between Day 3 and Day 5 after admission in the palliative care unit and 6 months after patient's death

Variables	OR (95% CI)	p-value
<i>Patients</i>		
Anxiety/psychology suffering on admission	1.59 (1.11–2.28)	0.01
<i>Relatives</i>		
Patient's surrogate	1.4 (0.97–2.02)	0.07
Admission to the palliative care unit requested by relatives	0.7 (0.48–1.03)	0.07

CI = confidence interval; OR = odds ratio.

Variables in the multivariable analysis on the basis of a *p*-value < 0.1 included the following: Center variables: beds > 15 in palliative care unit, 24 hours visitation policies, family on-site sleep in a dedicated room, information of relatives with a formal meeting at patient's death, sending a condolence letter, presence of a grieving support group after death for relatives, presence of a mourning follow-up, and delivery of an information leaflet at patient's death. Patients' variables: single patient, age, duration of the cancer history. Relatives' variables: primary caregiver, relative gender, level of education equal or superior to bachelor, previous palliative care hospitalization for a close relative, presence at home of a health-care worker or a life support person or support hospital service.

in population included (size of the sample) may explain the conflicting results. It seems important to tailor to the relative's needs during illness trajectory, knowing that needs vary according to illness trajectory. Relative's needs were more focused on information, on treatment possibilities and side effects (92.8%), diagnosis (91.6%), testing (91.1%), and physical symptoms (90.9%) following diagnosis of cancer (Ndiok and Ncama 2018). During the late phase of illness, insight into the gravity of the illness, participation in care, knowledge of similar situations in participants, and sense of safety in relation with the patient care became more important needs for relatives (Henriksson and Andershed 2007).

There have been few studies examining the prevalence of post-traumatic stress disorder symptoms in relatives after an expected death in palliative care units (Hirooka et al. 2017a, 2018b). Given that trauma symptoms may be distinct from PG reactions (Horowitz et al. 1997) but may be highly interconnected (Hirooka et al. 2017), we found that 53.2% of relatives had post-traumatic stress disorder symptoms 6 months after patient's death. Young patient age, psychological suffering in patient on admission, being a female partner, or being a patient's child were found to be independent factors at risk of having post-traumatic stress disorder symptoms. Being provided the opportunity as relatives to sleep on site in a dedicated room and to contribute to the physical preparation of the body for funerals were independent factors of decreasing post-traumatic stress disorder symptoms. These two factors explained the importance for relatives to have the opportunity of saying properly goodbye and of staying close to their loved one during the important moment of the transition from life to death. Sending a condolence letter is a matter of debate in palliative care (Hayward et al. 2016; Porter et al. 2021). Half of our units did it. This study showed no benefit of relatives who received a condolence letter contrasting to other study who reported an increase of post-traumatic stress disorder symptoms in different setting (Kentish-Barnes et al. 2017).

Given the results of this study reporting high distress in most relatives 6 months after patient's death, prevention strategies should be discussed. Although several interventions conducted in outpatient cancer improved relatives' outcomes while the patient was alive (Dionne-Odom et al. 2015a, 2016b), conflicting preventive measures were reported in relatives' bereavement

outcomes. A proactive randomized communication intervention to help patients/relatives to ask questions, express concerns, and help oncologist to address them effectively did not significantly improve mental health, anxiety, depression symptoms, or PG reactions 7 months after patient's death (Duberstein *et al.* 2019). A randomized trial including bereaved individuals, at risk for PG, 8 months after loss, reported significant efficacy of a cognitive-behavioral therapist-assisted-internet delivered intervention on PG, anxiety, depression, and PTSD (Litz *et al.* 2014). Research on internet-based grief therapy is ongoing (Hoffmann *et al.* 2018). This study contributes data that suggest a profile at high-risk relatives of PG. Screening symptoms suggestive of anxiety and depression shortly after patient admission, taking care of relatives of patients with respiratory symptoms, or psychological suffering might alleviate the burden of relatives. The qualitative part of our study, interviewing relatives with PG, should add insights into the improvement of the bereavement process.

This study has several strengths and limitations. The multicenter design and the high number of included relatives and their high response rate at 6 months provide a large overview of post-loss relatives' conditions. We chose to include all relatives willing to participate, providing a potentially broad panel of individual consequences according to their relationship with the patient. This study has several limitations. First, only 24% of invited centers participated in the study, mainly due to fear of physicians to include relatives in a bereavement research project, which contrasts with the reportedly beneficial effects of participating in research for bereaved relatives (Kentish-Barnes *et al.* 2015). However, participating centers were representative of the current practice for family-centered care in France (Rhondali *et al.* 2014). Second, grief is a complex phenomenon, and components of psychological distress may not have been sufficiently taken into account in the different statistical models. Third, this study was performed in France and the results may not be generalizable to other European and non-European culture settings (Avidan *et al.* 2021).

Conclusions

Six months after the death of a loved one with cancer in palliative care units in France, one-third of relatives were still suffering of complicated grief and half of them had a post-traumatic stress disorder. No recommendations are currently available to prevent these psychological consequences. Thus, this study represents the first step of a potential process of prevention of PG. The next step in our study, the testimony of relatives who have experienced this trauma, will help to define other improvement strategies.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/S1478951523000111>.

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committee on 20 March 2018 and 4 March 2019 and the CNIL (Commission Nationale de l'Informatique et des Libertés; number 918120, on 15 June 2018). In accordance with French law, patient's data are collected following the criteria of certificate of conformity MR003.

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