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Clinical Paper

Prevalence and risk factors for post-traumatic stress disorder in relatives of out-of-hospital cardiac arrest patients☆

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ABSTRACT

Aim: Prognostic uncertainty and surrogate decision-making demands associated with prolonged unconsciousness in out-of hospital cardiac arrest (OHCA) patients in the intensive care unit (ICU) may increase post-traumatic stress disorder (PTSD) risk in their relatives. Our aim was to study PTSD frequency and risk factors in relatives of OHCA patients.

Methods: In this observational study 101 consecutive eligible adult relatives of OHCA patients were interviewed using validated questionnaires, the "Impact of Event Scale-Revised" to detect PTSD and the "Family-Satisfaction with Care in the ICU" to assess potential PTSD risk factors.

Results: PTSD was detected in 40/101 relatives (40%). Multivariate logistic regression identified three significant PTSD predictors [odds ratio, 95% confidence interval]: female gender [3.30, 1.08–10.11], history of depression [3.63, 1.02–12.96], family perception of the patient's therapy as insufficient [18.40, 1.52–224.22]. Three other predictors were not significantly associated with PTSD (hypothermia treatment of the patient [2.86, 0.96–8.48]), delayed delivery of prognostic information by ICU staff [2.11, 0.83–5.38], family-ICU staff conflict [3.61, 0.71–18.40]). A prediction rule including six factors ($p < 0.15$ each) showed high discrimination (area under the receiver-operating characteristic curve 0.74) with a stepwise increase in risk for PTSD from 0% (no risk factor) to 63% (≥3 risk factors). There was no evidence for effect modification either by survival status or neurological outcome.

Conclusion: Relatives of OHCA patients treated in the ICU are at increased risk of PTSD, which can be predicted based on six factors, three ICU-related and potentially at least partly modifiable. Further research is needed to validate our findings and to develop strategies to prevent PTSD in OHCA patients' relatives.

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1. Introduction

In recent years, healthcare workers in critical care settings have broadened their focus from a "disease-only" approach to a patient- and family-centered approach.[1–3] Intensivists increasingly have recognized that relatives facing a critically ill loved one experience considerable stress, which may translate into morbidity and mortality.[4,5] Studies of family members of patients in the general ICU population[6,7] have shown these relatives to be at high risk for a variety of adverse psychological outcomes that collectively, have been termed post-intensive care syndrome-family.[8] These outcomes include anxiety, depression, complicated grief, acute stress disorder and post-traumatic stress disorder (PTSD).

Posttraumatic stress disorder is a syndrome lasting at least four weeks, comprising three types of response to a traumatic event or situation: (1) unwanted recollection, e.g., in nightmares or flashbacks, (2) strong avoidance of reminders of the trauma, and (3) physiological hyperarousal, e.g., insomnia, irritability, difficulty concentrating, or hypervigilance.[9] PTSD significantly decreases functioning and quality-of-life,[6,7] and has been associated with poor health behaviors, among them physical inactivity, medication nonadherence, and more intense smoking,[10] and with increased rates of unemployment, poverty, medical care utilization including hospital admission, and suicide.[11] Moreover, PTSD has been linked to elevated risk of gastritis, stomach ulcer, arthritis, metabolic conditions, and, particularly, cardiovascular disease including fatal

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cardiac events.[12–14] By definition, PTSD manifests at least one month after the precipitating trauma, but it may emerge months later.

PTSD appears to be substantially more frequent in family members of ICU patients than in the general population. Symptoms consistent with the syndrome were detected in roughly 30% of relatives within 3 months after conclusion of their loved one's ICU stay; higher prevalence – up to 50% – was found in relatives who felt that they received incomplete information regarding their family member's case or whose loved one succumbed in the ICU.[7] The highest PTSD prevalence – 60% – was seen in relatives of patients dying in the ICU after end-of-life decision-making, especially when communication with ICU staff was perceived to be suboptimal.[15] By contrast, lifetime PTSD prevalence has been estimated at ~8% in the US general population.[11]

Given PTSD epidemiology in family members of ICU patients and the characteristics of out-of-hospital cardiac arrest (OHCA) patients, relatives of the latter may be at particularly high risk of PTSD. Due to their severe condition and hypothermia treatment, OHCA patients typically are unconscious during their initial days in critical care, prolonging the period of prognostic uncertainty and forcing relatives to act as surrogate decision-makers.[16] Moreover, adverse neurological outcomes and death in the ICU or ward are frequent in OHCA patients.[17]

However, to the best of our knowledge, little if any published research has examined prevalence of or risk factors for PTSD in families of OHCA patients. Data on these topics would be valuable, since the literature on PTSD in general[9] and in relatives of patients in the general ICU population suggest that the syndrome may be treatable or even preventable: for example, an interventional trial demonstrated that a proactive communication strategy improved outcomes of ICU patients' family members regarding PTSD as well as anxiety and depression.[18]

We therefore conducted this observational cohort study to (1) assess the risk of PTSD in relatives of OHCA patients following the patients' ICU stay and (2) investigate factors predicting this adverse outcome. We hypothesized that an inadequate relative-health care worker interaction, i.e., deficient communication with the ICU team or family member dissatisfaction with care and decision-making associated with their loved one's ICU stay, would predict PTSD in family members. Such knowledge will enable development of a clinical prediction rule for PTSD in this setting, as well as communication strategies and psychosocial support strategies which in the near future, may be assessed in prospective interventional trials to improve the relatives' outcomes.[19]

2. Methods

2.1. Setting, subjects and ethics

This study sought to include one relative each of consecutive patients admitted to the ICU of the University Hospital, Basel, Switzerland, between January 2007 and August 2012 for treatment of OHCA. To be eligible, the relative had to have served as a surrogate decision-maker for the patient and to speak a local language. The study was approved by the local Ethic Committee and all relatives and patients gave written informed consent.

2.2. Study design

Using a list assembled through our electronic ICU registry, between October 2012 and January 2013, we telephoned eligible patients and relatives to invite participation in the study. If patients were deceased or otherwise could not be reached, we called their relatives listed in the clinical documentation as next-of-kin. Relatives were recruited according to criteria of a previous study,[7] i.e., by surrogate decision-making rank (spouse > parents/children > others); if a relative was unavailable to participate, we contacted the family member(s) next in rank.

Baseline data as well as hospital outcomes of consenting patients were collected by abstraction from the electronic registry. After recruitment, family members were interviewed by telephone using validated structured questionnaires described below. To maximize methodological consistency and thereby decrease bias, all family member interviews were conducted by a single physician (MZ) using the same content sequence and study instruments as defined below. Each family member interview typically took between 30 and 60 min.

2.3. Study instruments

The validated German version of the Impact of Event Scale-Revised (IES-r) questionnaire[20] was used to detect and measure PTSD symptoms. The original IES-r was designed for generic application after any type of traumatic event, and is well-validated, including for use in different languages (including German language[21]) and also in telephone interviews.[7,22] Each questionnaire administration is anchored to an index traumatic event, in this case, the loved one's ICU stay for treatment of OHCA. The instrument asks about 22 potential psychological or physical responses to the index event, which are grouped into one of the three subscales, "intrusion" (7 items), "avoidance" (8 items), and "hyperarousal" (7 items). The frequency of each response is rated on the scale, 0, "not at all," 1, "rarely," 3, "sometimes," or 5, "often."

For our study, we used the German translation of the IES-r, which was previously validated in two independent samples and compared with structured clinical interviews for the diagnosis of PTSD.[21] As suggested, a final IES-r score was calculated using the following validated equation: "$-0.02 \times$ intrusion subscale score $+ 0.07 \times$ avoidance subscale score $+0.15 \times$ hyperarousal subscale score $- 4.36$".[21] In patients with scores >0, PTSD can be diagnosed with high specificity (89%) and sensitivity (79%).[21]

To measure relatives' satisfaction with the index critical care experience and to specifically identify their expectations and needs regarding communication and interaction with the ICU team, we used an expanded German-language version of the Family Satisfaction with Care in the Intensive Care Unit questionnaire (FS-ICU).[3,23] The FS-ICU is a well-validated 24-item instrument designed to measure two main domains: (1) the patient's and family members' overall satisfaction with care as well as with environmental factors in the ICU (14 items) and (2) satisfaction, expectations, and needs regarding information transfer and decision-making during the patient's ICU stay (10 items).[3,23–26] Each item is rated on a 0–100% scale, with higher scores denoting greater satisfaction. We expanded the questionnaire with 18 questions regarding communication and interaction with the ICU team (Table 3) which were developed through rounds of consensus conferences within the research team. In each round, potential new items were assessed for content validity and clarity by independent physicians, whose feedback was incorporated to reword the items until ambiguous phrasing was eliminated.

2.4. Patient outcome assessment

In the interview, subjects also were asked about patient outcomes as of that telephone conversation, including death from any cause and neurological status as described in the Cerebral Performance Category scale (CPC).[27] CPC scores range from 1, no neurologic disability; 2, moderate disability including hemiplegia, seizures, ataxia, dysarthria, dysphasia, memory loss, or other mental changes, but sufficient cerebral function to live independently

and work at least part-time; 3, severe neurological impairment leaving the patient dependent on others for daily support; 4, a vegetative state; or (5) death. We classified neurological outcomes as "good," i.e., a CPC score of 1 or 2, or "poor," a score of 3–5 also including non-survivors.

2.5. Statistics

The main purpose of this analysis was to identify predictors of PTSD in relatives of patients treated in the ICU for OHCA. As potential predictors, we tested a variety of items within three domains, namely (1) patient characteristics, e.g., age, gender, medical conditions, treatment and outcomes; (2) family member characteristics, e.g., socio-demographic variables including marital status, past medical history of depression, and (3) ICU-related factors, e.g., expanded FS-ICU questionnaire items; since responses to FS-ICU questions were generally skewed to favorable ratings, we dichotomized each of these items into "high satisfaction" or "low satisfaction" as done in previous research.[25]

We performed univariate and multivariate logistic regression modeling to study independent associations between these potential predictors and PTSD in relatives, calculating odds ratios (ORs) and their 95% confidence intervals (CIs). This analysis first was performed within each of the three domains. All items found to have a p value ≤ 0.2 then were assessed in an overall multivariate model. To study the potential benefit of these factors, we also calculated a simple prediction rule giving one point for each risk factor. We calculated the area under the receiver operating characteristics curve (AUC) to study discrimination of this rule. To look for subgroup effects and effect modifications, we also included interaction terms into the models, i.e., we studied whether fatal patient outcome changed the associations.

To characterize the relative and patient samples, we present descriptive statistics with the mean and standard deviation (SD) or median [interquartile range, IQR, 25th–75th percentiles] as appropriate. Statistical analyses were conducted using Stata 11 software (Stata Corp, College Station, Texas, USA). A p value < 0.05 was considered to be significant and a p-value between 0.05 and 0.15 was considered to be a trend. All p values were two-tailed.

3. Results

3.1. Study sample

A total of 199 OHCA patients were treated in our ICU during the study period, of whom 72 (36%) had relatives unable to speak local languages or unreachable by phone, and 26 (13%) had relatives who refused informed consent. The remaining 101 patients (51%) had a relative included in this analysis.

As seen in Table 1, participating relatives were mainly middle-aged or elderly female spouses or adult children. Patients were mainly middle-aged or elderly men, about two-thirds of whom underwent hypothermia treatment and nearly all of whom were intubated and had vasopressor support. The mean time since cardiac arrest was 2.6 years (SD ± 1.7). There was no association between time since cardiac arrest and risk of PTSD ($p = 0.33$).

3.2. Patient and relative outcomes

The overall rate of poor neurological outcome as defined by a CPC Score ≥3 was 61% including death in 56% of patients. Therefore 39% of the patient samples were long-term survivors without severe neurological sequelae.

In total, 40 relatives (40%, 95% confidence interval [CI] 30–49%) had PTSD. Compared to those without this condition, relatives with PTSD significantly more often consulted a psychologist/psychiatrist (13% [8/61] vs 33% [13/40], $p = 0.02$) and significantly more often took newly prescribed psychotropic drugs, i.e., anti-depressive medication, (13% [8/61] vs 40% [16/40], $p = 0.003$) after their loved one's index OHCA treatment in the ICU.

Table 1
Patient and relative characteristics.

Relative characteristics, % (n) unless otherwise stated	$n = 101$
Demographics	
Age, years, mean ± SD	58.1 ± 12.2
Age, years, median (IQR)	58 (46–70)
Female	70% (71)
Education	
High school diploma	9% (9)
Higher education (college degree)	83% (84)
University degree (graduate degree)	8% (8)
Job Situation	
Salaried employee	56% (57)
Retired	33% (33)
Other	11% (11)
Changed work due to patient's OHCA	6% (6)
Relationship to patient	
Spouse	71% (72)
Parent	3% (3)
Sibling	4% (4)
Adult child	17% (18)
Other	4% (4)
Patient characteristics, % (n) unless otherwise stated	**$n = 101$**
Demographics	
Age, years mean ± SD	63.4 (±15.4)
Age, years, median (IQR)	63 (48–79)
Female	33% (33)
Treatment	
Hypothermia	67% (68)
Intubation	99% (100)
Vasopressors	93% (94)
Impella device	17% (17)
Cardiac catheterization	70% (71)
Time since cardiac arrest (years) mean ± SD	2.6 (1.7)
Long-term outcome	
Poor neurological outcome (CPC score 3–5)	61% (62)
Mortality	56% (57)

CPC, cerebral performance category; OHCA, out-of-hospital cardiac arrest; IQR, interquartile range; SD, standard deviation.

3.3. Univariate associations of potential predictive factors with PTSD

In a first step, we assessed univariate associations with PTSD within each of three domains: relative and patient characteristics (Table 2) and factors associated with ICU care (Table 3). The univariate analysis identified several family member characteristics associated with PTSD: female gender (OR 2.85, 95% CI 1.09–7.50), living with the patient (OR 4.73, 95% CI 1.48–15.08), and history of depression before the patient's OHCA (OR 3.25, 95% CI 1.01–10.56). Similarly, several patient characteristics had univariate associations with PTSD, including younger age (OR per decade of age 0.98, 95%CI 0.95–1.00) and salaried employment before the index OHCA (OR 3.08, 95%CI 1.34–7.04). Also, longer ICU stays (OR per ICU day 1.07, 95%CI 0.98–1.16), hypothermia treatment (OR 2.23, 95%CI 0.91–5.51), and infection requiring antibiotics (OR

Table 2
Univariate associations of relative and patient characteristics with PTSD in family members of OHCA patients.

Factor	No PTSD ($n=61$)	PTSD ($n=40$)	Univariate odds ratio (95%CI)	p
Relatives characteristics, % (n) of subgroup unless otherwise stated				
Female	62% (38)	82.5% (33)	2.85 (1.09–7.50)	0.033
Age, years, mean ± SD	59.5 ± 12.3	56 ± 11.8	0.98 (0.94–1.01)[a]	0.152
Spouse of patient	66% (40)	80% (32)	2.10 (0.82–5.36)	0.121
Adult child of patient	23% (14)	10% (4)	0.37 (0.11–1.23)	0.105
Lives with patient	66% (40)	90% (36)	4.73 (1.48–15.08)	0.009
Has children	71% (43)	75% (30)	1.26 (0.51–3.10)	0.621
Education				
High school diploma	7% (4)	13% (5)	2.04 (0.51–8.10)	0.313
Higher education (college)	84% (51)	83% (33)	0.92 (0.32–2.67)	0.884
University degree (graduate degree)	10% (6)	5% (2)	0.48 (0.09–2.52)	0.387
Job situation				
Salaried employee	54% (33)	60% (24)	1.27 (0.57–2.86)	0.559
Retired	39% (24)	23% (9)	0.45 (0.18–1.10)	0.081
Past medical history				
Depression	8% (5)	23% (9)	3.25 (1.01–10.56)	0.050
Patient characteristics, % (n) of subgroup unless otherwise stated				
Female	38% (23)	25% (10)	0.55 (0.23–1.33)	0.186
Age, mean ± SD	65.5 ± 15.1	60.4 ± 15.7	0.98 (0.95–1.00)	0.105
ICU length-of-stay, days, mean ± SD	5.2 ± 4.5	6.8 ± 5.3	1.07 (0.98–1.16)	0.122
Hospital length-of-stay, days, mean ± SD	10.3 ± 10.2	10.7 ± 11.2	1.00 (0.97–1.04)	0.852
Initial APACHE II score, mean ± SD	24.2 ± 6.0	23.7 ± 6.9	0.99 (0.93–1.05)	0.716
Initial SAPS II score, mean ± SD	62.1 ± 14.9	59.8 ± 17.0	0.99 (0.96–1.02)	0.483
Outcome				
In-hospital mortality	46% (28)	38% (15)	0.71 (0.31–1.60)	0.404
Long-term[a] mortality	62% (38)	48% (19)	0.55 (0.24–1.23)	0.144
Poor neurological outcome (CPC score 3–5)	62% (38)	60% (24)	0.91 (0.40–2.06)	0.817
Therapy				
Hypothermia	61% (37)	77% (31)	2.23 (0.91–5.51)	0.081
Intubation	98% (60)	100% (40)	NA	NA
Vasopressors	95% (58)	90% (36)	0.47 (0.10–2.20)	0.335
Antibiotics	49% (30)	65% (26)	1.92 (0.84–4.36)	0.120
Impella device	19% (9)	20% (8)	1.44 (0.51–4.12)	0.492
Hemofilter	7% (4))	8% (3)	1.14 (0.24–5.37)	0.873
Cardiac catheter	71% (43)	70% (28)	0.98 (0.41–2.34)	0.958
Rehabilitation, days, mean ± SD	22.5 ± 28.5	57.1 ± 72.1	1.01 (1.00–1.03)	0.076
Socio-economic factors				
Live in partnership	67% (41)	85% (34)	2.76 (1.00–7.66)	0.051
Had children	77% (47)	73% (29)	0.79 (0.31–1.96)	0.605
Education				
High School diploma	20% (12)	15% (6)	0.72 (0.25–2.11)	0.550
Higher education	69% (42)	73% (29)	1.19 (0.49–2.88)	0.695
College degree	8% (5)	10% (4)	1.24 (0.31–4.95)	0.756
Advanced degree	3.% (2)	3% (1)	0.76 (0.07–8.63)	0.822
Job before OHCA				
Employed	33% (20)	60% (24)	3.08 (1.34–7.04)	0.008
Retired	62% (38)	40% (16)	0.40 (0.18–0.91)	0.030

APACHE, acute physiology and chronic health evaluation severity score; CI, confidence interval; CPC, cerebral performance category; ICU, intensive care unit; OHCA, out-of-hospital cardiac arrest; PTSD, post-traumatic stress disorder; SAPS, simplified acute physiological score; SD, standard deviation.
The odds ratio compares the PTSD risk conferred by a potential predictor to the PTSD risk in the absence of the predictor.
[a] Per decade.

1.92, 95%CI 0.84–4.36) tended toward association with PTSD. In-hospital patient mortality as well as long-term patient mortality were not associated with relatives' PTSD (OR 0.71, 95%CI 0.31–1.60, $p=0.40$ and OR 0.55, 95%CI 0.24–1.23). In univariate analysis, three ICU-related factors were associated with PTSD: longer time to receive initial information (OR per post-admission hour 1.18, 95%CI 0.93–1.50); conflict with ICU staff (OR 3.35, 95%CI 0.79–14.29) and relatives' perception that therapeutic measures were insufficient (OR 6.56, 95%CI 0.71–60.98). Although there was no association between provision vs non-provision of prognostic information and PTSD, the PTSD risk increased when the provided information was perceived as being unhelpful (OR 2.55, 95%CI 0.83–7.59) or inaccurate (OR 3.52, 95%CI 0.96–12.87). Family member participation in decision-making about withdrawing medical intervention was not associated with PTSD (OR 1.00, 95%CI 0.50–2.20); yet, if relatives disagreed with the physician's withdrawal of medical intervention, the risk for PTSD tended to increase (OR 2.27, 95%CI 0.50–9.70).

3.4. Multivariate analyses and clinical prediction rule

We performed multivariate logistic regression analysis of all factors found in univariate analysis to be associated with PTSD in relatives of OHCA patients with a $p \leq 0.2$. In the multivariate analysis, three factors were significant predictors of this outcome with p values < 0.05 (Table 4): female gender of the relative (OR 3.30, 95%CI 1.08–10.11), history of depression in the relative (OR 3.63, 95%CI 1.02–12.96), therapeutic measures perceived as being insufficient [18.40, 1.52–224.22). Three other factors had no significant association with PTSD: hypothermia treatment of the patient (OR 2.86, 95%CI 0.96–8.48]), a long interval until the relative received

Table 3
Univariate association of ICU-care related factors and PTSD in family members of OHCA patients.

ICU care-associated factors, % (*n*) of subgroup unless otherwise stated	No PTSD (*n* = 61)	PTSD (*n* = 40)	Univariate odds ratio (95%CI)	*p*
Factors related to staff-family communication				
Family satisfaction with early communication (0, least to 100%, most)	80.1 ± 18.2%	75.7 ± 22.6%	0.99 (0.97–1.01)	0.290
Time delay to get information from ICU staff, hours	1.0 ± 1.2	5.9 ± 16.2	1.18 (0.93–1.50)	0.167
Family informed about expected risks and prognosis on admission	80% (48/60)	83% (33/40)	1.18 (0.42–3.31)	0.755
If yes, information was unhelpful	15% (7/48)	30% (10/33)	2.55 (0.83–7.59)	0.094
If yes, information was inaccurate	8% (3/48)	24% (8/33)	3.52 (0.96–12.87)	0.057
Getting a number for good or bad outcome on admission	9% (5/58)	5% (2/40)	0.56 (0.10–3.03)	0.499
Information changed relatives' opinion on patient's treatment	9% (5/54)	19% (7/37)	2.29 (0.67–7.86)	0.189
Physician spoke openly about the situation	92% (55/60)	88% (35/40)	0.64 (0.17–2.36)	0.499
Relative perceived therapeutic measures as sufficient	98% (59/60)	90% (36/40)	0.15 (0.02–1.42)	0.098
Enough time to get information	92% (55/60)	85% (34/40)	0.52 (0.15–1.82)	0.303
Information was easy to understand	93% (56/60)	90% (36/40)	0.64 (0.15–2.73)	0.550
Information covered all points of interest	93% (56/60)	90% (36/40)	0.64 (0.15–2.73)	0.550
Felt in conflict with the ICU staff	5% (3/60)	15% (6/40)	3.35 (0.79–14.29)	0.102
Symptoms were not under control	12% (7/60)	5% (2/40)	0.40 (0.08–2.03)	0.267
Relative felt guilty	10% (6/60)	13% (5/40)	1.29 (0.36–4.54)	0.696
Relative could name his/her emotions	75% (45/60)	68% (27/40)	0.69 (0.29–1.67)	0.414
To withdraw medical intervention was a topic	55% (33/60)	55% (22/40)	1.00 (0.45–2.23)	1.000
If yes, relative shared physician's opinion	88% (29/33)	73% (16/22)	0.44 (0.10–1.88)	0.269
Selected additional FS-ICU items				
Decision-making process ("lower satisfaction")				
Inclusion in decision-making	19% (10/53)	28% (10/36)	1.65 (0.61–4.51)	0.325
Time involved in decision-making	28% (15/54)	39% (14/36)	1.65 (0.68–4.06)	0.271
Information to participate in decision-making	11% (6/54)	19% (7/36)	1.93 (0.59–6.31)	0.276
Time to think about decision-making	9% (5/55)	14% (5/36)	1.61 (0.43–6.03)	0.477
Support during decision-making	24% (13/55)	19% (7/36)	0.78 (0.28–2.19)	0.637
Control over the care	6% (3/53)	8% (3/36)	1.52 (0.29–7.97)	0.624
Amount of hope given	16% (9/55)	31% (11/36)	2.25 (0.82–6.15)	0.115
Overall satisfaction with decision-making	4% (2/55)	8% (3/37)	2.34 (0.37–14.73)	0.366

CI, confidence interval; FS-ICU, family satisfaction-intensive care unit questionnaire; ICU, intensive care unit; PTSD, post-traumatic stress disorder.
The odds ratio compares the PTSD risk conferred by a potential predictor to the PTSD risk in the absence of the predictor. [a] Per hour.

Table 4
Multivariate analysis: independent predictors of PTSD in family members of OHCA patients.

	Odds ratio (95% CI)	*p*	AUC
Model 1. Relative characteristics			
Female gender	2.97 (1.10–8.00)	0.032	0.65
History of depression	3.43 (1.02–11.61)	0.047	
Model 2. Patient characteristics			
Hypothermia treatment	2.23 (0.91–5.51)	0.081	0.58
Model 3. ICU care-related factors			
Time delay after patient's ICU admission until relative gets information from ICU staff (per hour)	1.24 (0.91–1.70)	0.164	0.68
Therapeutic measures perceived as insufficient by relative	7.93 (0.82–76.93)	0.074	
Conflict between relative and ICU staff	3.32 (0.70–15.73)	0.130	
Model 4. All factors in models 1–3			
Female gender of relative	3.30 (1.08–10.11)	0.037	0.77
History of depression in relative	3.63 (1.02–12.96)	0.047	
Hypothermia treatment of patient	2.86 (0.96–8.48)	0.058	
Time delay for relative to get information from ICU staff (per hour)	2.11 (0.83–5.38)	0.119	
Therapeutic measures perceived as insufficient by relative	18.40 (1.52–224.22)	0.022	
Conflict between relative and ICU staff	3.61 (0.71–18.4)	0.122	

AUC, area under the receiver-operating characteristic curve (measure of diagnostic accuracy); CI, confidence interval; ICU, intensive care unit; OHCA, out-of-hospital cardiac arrest; PTSD, post-traumatic stress disorder.
The multivariate analysis included all potential predictive factors for PTSD in relatives found in previous univariate analyses to have a $p \leq 0.2$. The odds ratio compares the PTSD risk conferred by a potential predictor to the PTSD risk in the absence of the predictor.

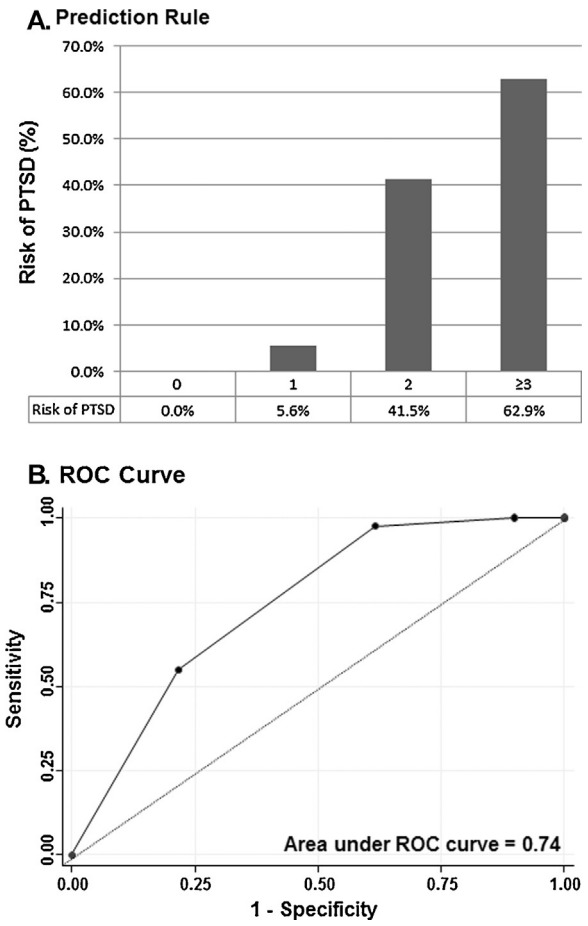

Fig. 1. Prediction rule for PTSD in family members of OHCA patients. (A) Increasing risk for PTSD in relation to increasing number of predictive factors. (B) Area under the ROC curve for the prediction rule for discrimination of relatives with and without PTSD. OHCA, out-of-hospital cardiac arrest; PTSD, post-traumatic stress disorder, ROC, receiver-operating characteristics.

prognostic information from ICU staff (OR 2.11, 95%CI 0.83–5.38), conflict with ICU staff (OR 3.61, 95%CI 0.71-18.40). There was no evidence for effect modification either by patient survival status or neurological outcome (data not shown).

A model including all predictors with $p < 0.15$ and their regression coefficients showed high discrimination in forecasting PTSD in relatives of OHCA patients, with an area under the receiver-operating characteristic curve (AUC) of 0.77 (95%CI 0.68–0.86). A simplified clinical prediction rule based on the factors alone also demonstrated good performance, with an AUC of 0.74 (95%CI 0.66–0.83) (Fig. 1A). PTSD risk in family members increased from 0% if none of the factors was present to 63% when 3 or more were present (Fig. 1B).

4. Discussion

The present study, to the best of our knowledge, the only systematic assessment to date of PTSD prevalence and risk factors in family members of OHCA patients, had three main findings. First, PTSD was common in this group – detected using a well-validated screening instrument, the IES-r, in 40% of subjects. These results are in line with those of French and US studies reporting PTSD in 33–49% of relatives of patients in end-of-life situations 90 days after the patient's hospital discharge or death in the ICU.[6,7,28]

Second, we identified six independent PTSD risk factors in family members of OHCA patients: (1) female gender of realtives; (2) history of depression in the relative, (3) hypothermia treatment of the OHCA patient, (4) long delay in the family's receiving prognostic information regarding their loved one from the ICU staff, (5) perceived insufficiency of the patient's therapeutic measures, and (6) family conflict with ICU staff. In general, these observations accord with the literature. For example, Azoulay et al. found higher PTSD risk in female relatives than in male relatives of French ICU patients.[7] Female gender also was identified as a PTSD risk factor in studies focusing on kin of patients in end-of-life situations or of patients with severe traumatic brain injury.[4,29] Depression has been reported as a lifetime comorbidity of PTSD.[30–32] Previous research has shown especially high PTSD rates (50% or 80%, respectively) in relatives who felt that they were given incomplete information regarding their loved one hospitalized in the ICU[7] or in relatives whose loved one died in the ICU after end-of-life decision-making.[7,18]

Our finding that hypothermia treatment of the OHCA patient is an independent risk factor for PTSD in his or her relative, although perhaps intuitive, is to our knowledge, novel. Based on the results of two randomized trials, hypothermia is thought to improve neurological outcomes in OHCA patients and is thus recommended in treatment guidelines.[16,33,34] Yet, because it entails intubation, and sedation, hypothermia prolongs unconsciousness for several days. The patient's uncertain prognosis during this time is highly stressful to family members, as is the required involvement in decision-making as patient surrogates – because post-OHCA morbidity remains high despite medical treatments, important decisions about reasonable measures and next steps must be made rapidly.

Our third main finding was an absence of association between death/neurological outcome of a patient and PTSD risk for relatives, or of any effect modification based on these variables. This observation appears to be counter-intuitive: one would think that the frequent permanent neurological deficits[35] and disability of OHCA survivors would put relatives at higher risk for PTSD. However, there is no consensus in the literature about the impact of patient outcomes on family members' psychological burden. For example, Anderson et al. investigated 50 relatives of US ICU patients and reported no correlation between patient death and relatives' PTSD.[28] In contrast, an earlier study of relatives of terminally ill patients found higher PTSD rates if patients died in the ICU.[7] Some studies looking at relatives' satisfaction with ICU care found no correlation with patient survival[25] or even higher satisfaction in family members of non-surviving patients.[36]

Our findings have important clinical relevance in at least two ways. First, combining the six independent risk factors that we identified for PTSD in relatives of OHCA patients into a simple prediction rule accurately identifies family members likeliest to suffer that adverse psychological outcome. Second, half of these risk factors, namely delayed delivery of prognostic information regarding their loved one from the ICU staff to the family, perceived insufficiency of the patient's therapeutic measures, and family conflict with ICU staff, appear to be at least partly modifiable. Proactive communication and collaboration may be key to such modification. In the general ICU patient population, structured communication with family members and their inclusion in decision-making regarding their loved one decreased the relatives' psychological burden.[7,37,38] Additionally, proactive communication with family members about end-of-life decisions dramatically decreased relatives' PTSD incidence.[18] Effective proactive communication strategies included an end-of-life family conference according to specific guidelines[39–42] concluded with provision of a brochure on bereavement. The effects of these and similar strategies on family member PTSD incidence in the OHCA setting should be evaluated in prospective interventional studies.

Improved prediction of OHCA patient outcomes also may help address ICU-related risk factors for family member PTSD. Previous studies have demonstrated that physicians are reluctant to provide

prognostic information to family members of ICU patients and that physicians do so in considerably variable fashion.[43–45] One important reason why physicians do not communicate prognosis with patients' loved ones may be prognostic uncertainty, especially early after OHCA. An OHCA outcome prediction score has been developed by Adrie et al. in France and validated in two geographically distinct tertiary care hospitals in the US.[27,46] This score showed a high prognostic accuracy with high positive predictive value in identifying OHCA patients at high risk of poor outcome. Yet, whether sharing prognostic information based on this score with family members will reduce their psychological burden also must be determined in prospective interventional trials.

Our study had several limitations. First, we used a screening questionnaire rather than a psychiatrist or psychologist interview to identify PTSD. However, that questionnaire, the IES-r is widely applied and well-validated, and has shown ≥90% diagnostic efficiency.[47] Additionally, our finding of significantly greater pyschologist/psychiatric consultations and psychotropic medication use following the patient's index ICU stay in our PTSD group compared to unaffected relatives, provides evidence of robust identification of the syndrome in this study. Second, we interviewed subjects at variable times after the index ICU stay, which may have caused recall bias. Yet, in an exploratory analysis, we did not find that the time interval was an effect modifier for our statistical models (data not shown). Third, we only included 51% of relatives (101/199) potentially eligible for the study, which may have led to selection bias. Also, we did not collect data on whether or not relatives were present during the cardiac arrest which may have increased the risk for PTSD independent of the ICU experience. Forth, three of the six predictors included in the prediction rule had no significant association with PTSD at the 0.05 alpha error which may be due to the limited sample size and thus low power of the study. Out findings need validation in a larger prospective cohort. Lastly, deriving from a single-center study, our findings may lack generalizability to other institutions and countries. Thus, the present analysis should be regarded as hypothesis-generating, and further multicenter and multinational studies are necessary to confirm and validate our findings.

5. Conclusions

Compared with lifetime prevalence rates separately documented in the general population, relatives of patients treated for OHCA in the ICU are at increased risk for PTSD. This adverse outcome appears to be associated with different risk factors particularly female gender and history of depression in the relatives, family perception of inadequate patient care. Importantly, some of these factors may be at least partly modifiable. Further research is needed to assess whether preventive strategies based on our findings improve outcomes of relatives.

Competing interest

None declared.

Author contributions

SH, MZ, WL, and SM conceived and designed the study and wrote the study protocol. MZ, KT, GMB, and SH collected data. MZ and SH performed the statistical analyses wrote the first draft of the manuscript. All authors amended and commented on the manuscript and approved the final version.

Conflict of interest statement

None declared.

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