

Original Article

Prevalence and risk factors for post-traumatic stress disorder in Japanese relatives of out-of-hospital cardiac arrest patients after receiving a pamphlet concerning the grieving process

Megumi Suzuki, Youichi Yanagawa,  Aya Sakamoto, Haruka Sugiyama, and Yoko Nozawa

Acute Critical Care Center, Shizuoka Hospital, Juntendo University, Izunokuni, Japan

Aim: To investigate the prospective frequency of post-traumatic stress disorder (PTSD) among relatives of sudden death patients following provision of a pamphlet explaining the stages of the complicated grief process and self-regulating techniques.

Methods: From May 2017 to February 2018, we prospectively and consecutively provided a pamphlet to relatives of out-of-hospital sudden cardiac arrest victims who failed to obtain spontaneous circulation. We investigated the psychiatric status of the bereaved relatives using the Impact of Event Scale – Revised (IES-R). An IES-R score over 24 was defined as PTSD.

Results: Fifty-four relatives of the 54 dead patients (victims) provided permission of entry to this research. All subjects and victims were Japanese. Among them, 24 subjects had an IES-R score of 0 and 5 (9.3%) had PTSD approximately 1 month after their bereavement. There were no relatives who received spontaneous psychiatric treatment. The IES-R scores for non-medical cardiac arrest, death inquests, and parent variables were significantly higher compared with medical cardiac arrest, no inquest, and no parent, respectively. The IES-R scores in those who were a child of the victim were significantly lower than in those who were not.

Conclusion: The present study showed that the frequency of PTSD was 9.3% at 1 month following bereavement among Japanese relatives of sudden death victims after an intervention. This frequency was minimal compared with previous reports.

Key words: cardiopulmonary arrest, grief reaction, Japanese, post-traumatic stress disorder

INTRODUCTION

POST-TRAUMATIC STRESS DISORDER (PTSD) is the most prevalent psychopathological consequence of exposure to traumatic events, such as violence, injury, death, and disaster.¹ The core features of PTSD are the persistence of intense, distressing, and fearfully avoided reactions to reminders of the triggering event, alteration of mood and

cognition, a pervasive sense of imminent threat, disturbed sleep, and hypervigilance.^{1,2} Previously, interventions provided shortly after exposure to trauma, such as psychological debriefing, a one-session intervention in which survivors' experiences during a traumatic event are reviewed and discussed shortly after the event, failed to prevent PTSD and could have harmful consequences.¹ In contrast, there is evidence that problem-based, patient-supportive care reduces the severity of PTSD symptoms after traumatic injury.¹ The death of a loved one is recognized as a potential risk for strong psychological trauma.³ However, there is no standard approach for relatives of sudden death patients and there are few prospective investigations into the frequency of PTSD among relatives of sudden death patients.⁴

The purpose of this study was to investigate prospectively the frequency of PTSD and assess the factors associated with PTSD among relatives of sudden death patients after an intervention, which involved providing a pamphlet that detailed the steps of the complicated grief process, and useful self-regulating techniques, such as deep breathing.

This paper was presented Resuscitation 2019 in Ljubljana, Slovenia.

*Corresponding: Youichi Yanagawa, MD, PhD, Acute Critical Care Center, Shizuoka Hospital, Juntendo University, 1129 Nagaoka, Izunokuni City, Shizuoka 410-2295, Japan. E-mail: yyanaga@juntendo.ac.jp.

Received 13 Feb, 2020; accepted 18 Jun, 2020

Funding information

This work received funding from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) Supported Program for the Strategic Research Foundation at Private Universities, 2015–2019.

METHODS

THIS PROSPECTIVE STUDY protocol was approved by the review board of Juntendo Shizuoka Hospital (approval number 446) and registered in UMIN Clinical Trials Registry (approval number UMIN000028128). (https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000032202).

The Acute Critical Care Center in Juntendo Shizuoka Hospital, a 577-bed hospital including 20 beds in the intensive care unit and 20 beds in the high-care unit for emergency patients of Juntendo University, is located in the Izu Peninsula in Shizuoka Prefecture (near Tokyo). There are two acute critical care centers in eastern Shizuoka that accommodate critically ill patients, such as those with cardiac arrest, unstable circulation, unconsciousness, acute coronary syndrome, stroke, severe wounded trauma, severe burns, or poisoning. Our hospital also has helicopter landing pads for the emergency medical system utilizing physician-staffed emergency helicopters in eastern Shizuoka Prefecture and serves a population of approximately 1.2 million.

From May 2017 to February 2018, we prospectively and consecutively provide a pamphlet to relatives of out-of-hospital cardiac arrest victims who failed to obtain spontaneous circulation by advanced cardiopulmonary resuscitation. The relatives were defined as those within the first degree of kinship or unmarried housemates. If there were multiple relatives, then we provided a pamphlet to only one key person (proxy). The pamphlet described the stages of the complicated grief process, which was translated into Japanese from the leaflet “Bereavement: key facts” provided by The Royal College of Psychiatrists (<https://www.rcpsych.ac.uk/expertadvice/translations/japanese/bereavementkeyfacts.aspx>), and self-regulating techniques, such as deep breathing. The Royal College of Psychiatrists is the main professional organization of psychiatrists in the UK and is responsible for representing psychiatrists, undertaking psychiatric research, and providing public information about mental health problems (<https://www.rcpsych.ac.uk/about-us/publications-and-books/journals/our-journals-at-a-glance>). The pamphlet reflects the best available evidence at the time of its production.

We also presented our research plan to check each subject’s psychiatric status approximately 1 month after the bereavement by telephone or direct communication. Among the relatives who provided permission for this research, who were included as subjects, we investigated the subject’s psychiatric status using the Impact of Event Scale-Revised (IES-R).⁵ The IES-R is a 22-item self-reporting measure that assesses subjective distress caused by traumatic events. Respondents are asked to identify a specific stressful life

event and then indicate how much they have been distressed or bothered by it within the past 7 days by each “difficulty” listed. Items are rated on a 5-point scale ranging from 0 (“not at all”) to 4 (“extremely”). The IES-R yields a total score (ranging from 0 to 88), and subscale scores can also be calculated for the intrusion, avoidance, and hyperarousal subscales. The IES-R has been used as a diagnostic tool for PTSD.^{6–8} The IES-R has also shown a high validity in various other populations.⁹ Exclusion criteria were: relatives who would not receive contact from our staff, or when there were no relatives of the victims. An IES-R score over 24 was defined as PTSD.

We investigated the relationship between the IES-R score and the age of the victim, sex of the victim (male versus female), cause of cardiac arrest (non-medical versus medical, suicide versus non-suicide), place of cardiac arrest (home versus non-home, public space versus non-public), witness of cardiac arrest by the subjects or not, death inquests or not, relationship between the victims and relatives (parent versus non-parent, spouse versus non-spouse, child versus non-child), and sex of the relatives (male versus female). The cause of cardiac arrest was determined based on the results of a hearing history, whole-body computed tomography, and/or blood examinations that are carried out routinely for all patients with cardiac arrest in our department.^{10,11}

Japanese methods of death inquests are unique and are still in developmental stages and are therefore not very systematic.¹² Death inquests were requested by the physician who judged the victim as dead. There are two different systems of death inquests (or postmortem examination) in Japan: criminal inspection and judicial autopsy from a criminal justice standpoint and, from a public health standpoint, administrative inspection and either administrative or consent autopsy. Judicial autopsy is carried out for cases that police judge to be criminal, based on their brief initial investigation (i.e., external examination of the body and situational investigations at scene or hearing from the witnesses and relatives of the victims). If the police determine the cause of death to be non-criminal, judicial autopsy is generally not carried out.

We used the JMP 12.0 statistical software program (SAS Japan, Tokyo, Japan) for statistical analyses. A correlation coefficient between the IES-R and age of the victims was used for the statistical analyses. Non-paired Student’s *t*-test concerning the IES-R score and the cause of cardiac arrest, suicide, place of cardiac arrest, witness collapse, inquest, relationship between the victim and the subjects, and sex of the subjects were used for the statistical analyses. *P*-values <0.05 were considered to be statistically significant. To select the predictive variables regarding PTSD, a

multivariate analysis using a logistic regression analysis was undertaken by the forced entry procedure using all of the variables mentioned above.

RESULTS

DURING THE INVESTIGATION period, 117 patients with sudden onset out-of-hospital cardiac arrest who failed to obtain return of spontaneous circulation were treated by staff at the Acute Critical Center in Juntendo Shizuoka Hospital. Among them, 54 relatives of 54 dead patients (victims) provided permission to participate in this research; these 54 relatives were included as subjects. All subjects and victims were Japanese. Among them, 24 subjects had an IES-R score of 0 and 5 (9.3%) subjects had PTSD at approximately 1 month after the bereavement. There were no relatives who received psychiatric treatment spontaneously. Among the 63 dead patients whose relatives did not provide permission for inclusion in this study, 18 did not actually have any relatives.

The relationship between IES-R scores and the age of the 54 victims is shown in Figure 1. There was negative correlation between score of the IES-R and the age of the 54 victims.

The results of the comparison of IES-R score with sex of the victims, cause of cardiac arrest, place of cardiac arrest, witness collapse, death inquests, relationship between the victims and relatives, and sex of the relatives are shown in Table 1. There was no significant difference concerning sex of the victims, place of cardiac arrest, witness collapse, or spouse. However, the IES-R score in relation to non-medical

cardiac arrest, death inquests, and parent (his or her child had died) was significantly higher in comparison with medical cardiac arrest, no inquest, and no parent, respectively. The IES-R score in children (whose parent had died) was significantly lower than that in non-children. The IES-R score in suicidal cardiac arrest and female relatives was higher than those with no suicidal cardiac arrest and male relatives respectively, but these differences were not significant. A multivariate analysis revealed no significant predictors of PTSD (IES-R over 24) (Table 2).

DISCUSSION

THIS IS THE first study to report the frequency of PTSD (9.3%) at 1 month following bereavement among Japanese relatives of sudden death victims after an intervention. The relatives were given a pamphlet describing the complicated grief process.

Recently, rates of survival and good cerebral performance following out-of-hospital cardiac arrest have improved due to the development of automated external defibrillators, advanced cardiac life support, and intensive care for post-anoxic encephalopathy. The number of reports concerning the frequency of PTSD or psychiatric problems among patients who survived, and with good cerebral performance, has also increased.^{13–16} However, few reports have investigated PTSD among relatives of individuals who died as a result of out-of-hospital cardiac arrest.^{16–20} Most of these reports focused on offering the opportunity for family to be present during cardiopulmonary resuscitation, and this procedure decreased the frequency of PTSD among the

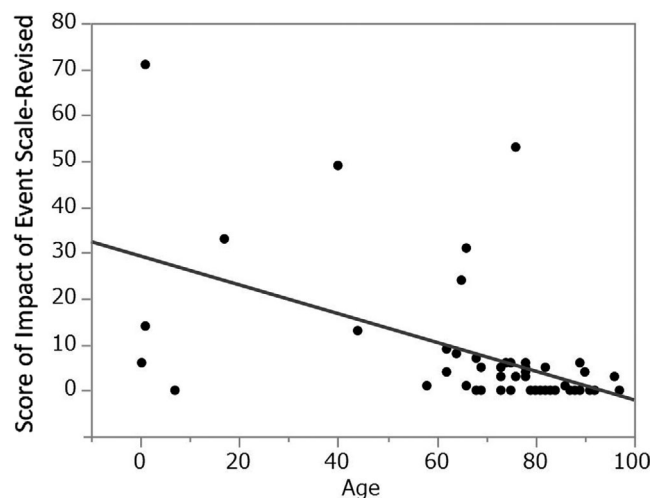


Fig. 1. Relationship between the age of out-of-hospital sudden cardiac arrest victims who died ($n = 54$) and the Impact of Event Scale – Revised (IES-R) score reported by a relative of each victim 1 month after bereavement. There was a negative correlation between IES-R score and the age of the victims. The correlation coefficient was -0.596 ($P < 0.0001$)

Table 1. Relationship between variables and Impact of Event Scale – Revised score reported 1 month after the death of a relative with out-of-hospital sudden cardiac arrest

Variable			P-value
Victim: sex	Male	Female	n.s.
	<i>n</i> = 32 8.1 ± 13.8	<i>n</i> = 22 5.9 ± 15.4	
Cause of death	Non-medical	Medical	<i>P</i> < 0.01
	<i>n</i> = 10 20.5 ± 23.9	<i>n</i> = 44 4.2 ± 9.3	
Suicide	Yes	No	<i>P</i> = 0.08
	<i>n</i> = 3 19.3 ± 16.5	<i>n</i> = 51 6.5 ± 14.1	
Place: home	Home	Non home	n.s.
	<i>n</i> = 40 7.6 ± 15.0	<i>n</i> = 14 8.0 ± 15.0	
Place: public	Public	Non-public	n.s.
	<i>n</i> = 10 8.0 ± 14.9	<i>n</i> = 44 7.0 ± 14.4	
Collapse witnessed by family	Yes	No	n.s.
	<i>n</i> = 42 7.5 ± 14.7	<i>n</i> = 12 6.3 ± 14.0	
Inquest post-mortem	Yes	No	<i>P</i> = 0.01
	<i>n</i> = 24 9.3 ± 12.7	<i>n</i> = 30 5.6 ± 15.7	
Relative: parent	Yes	No	<i>P</i> = 0.01
	<i>n</i> = 6 22.8 ± 26.1	<i>n</i> = 48 5.3 ± 11.3	
Relative: spouse	Yes	No	n.s.
	<i>n</i> = 31 7.5 ± 13.5	<i>n</i> = 23 6.7 ± 15.9	
Relative: child	Yes	No	<i>P</i> < 0.01
	<i>n</i> = 14 0.9 ± 1.9	<i>n</i> = 40 9.4 ± 16.2	
Relative: sex	Male	Female	<i>P</i> = 0.1
	<i>n</i> = 20 2.8 ± 5.4	<i>n</i> = 34 9.8 ± 17.3	

n.s., not significant.

bereaved family.^{4,15,16,20} We summarize the frequency of PTSD among bereaved families in Table 3 using our results and previous reports. However, the definition of PTSD based on the IES-R score and timing of investigation differed between reports. Previous studies showed the frequency of PTSD among bereaved families was 9–44%; our results were at the minimum of this range. Our period of investigation, at 1 month following bereavement, was the earliest. Generally, long duration from bereavement tends to

Table 2. Multivariate analysis of variables associated with Impact of Event Scale – Revised scores reported 1 month after the death of a relative with out-of-hospital sudden cardiac arrest

Variable	Odds ratio	95% confidence interval	P-value
Relative: sex	7.94e-26	0–48.7	0.09
Non-medical/medical	4.9e-19	–7.99	0.14
Victim: Age	1.12	0.94–1.54	0.21
Spouse/non-spouse	2.37e-9	0–68.9	0.57
Collapse witnessed by family	3.85	2.95e-5–5891	0.72
Death inquests	1.53	0.01–180.5	0.83
Public/non-public	2.16e + 42	0.00	0.99
Home/non-home	7.51e + 23	0.00	0.99
Victim: sex	0.000	–	0.99
Relative: child	0.01	0.00	0.99
Relative: parent	431.6	0.00	0.99
Suicide/non-suicide	1.45	–	0.99

The multivariate analysis revealed no significant predictors of post-traumatic stress disorder. Extremely unbalanced numbers between the objective and explanatory variable results thus produced unstable results. –, acalculia.

decrease the frequency of PTSD because spontaneous remission of PTSD is associated with length of time since trauma.^{1,21} In addition, we selected the minimum level of score (IES-R >24) as the definition of PTSD among the reports in Table 2, representing the loosest definition of PTSD. Accordingly, our minimum frequency of PTSD from bereavement is not based on timing of investigation and definition of PTSD. Whealin *et al* reported results of a study that examined risk and resilience factors associated with PTSD in an ethnographically diverse sample of Hawaii National Guard members comprised of Native Hawaiians, Filipino Americans, Japanese Americans, and European Americans.²² As a result, when controlling for other variables, they identified that Japanese Americans had an inverse relation to PTSD when compared to other nationalities. This difference of ethnicity in relation to tolerance for stress could explain low prevalence of PTSD after bereavement in this study. In addition, we provided a pamphlet that described the grief process and self-regulating techniques. This intervention might reduce the frequency of PTSD in relatives after bereavement. However, as we did not undertake a randomized study to determine the effect of the distribution of the pamphlet to bereaved relatives, we could not conclude that

Table 3. Frequency of post-traumatic stress disorder (PTSD) among bereaved families in previous reports

Primary author	PTSD	Time of evaluation	Subject	Number	Frequency (%)
Jabre	IES >30	90 day	Adult relatives of CPA		
			CPR witness	266	27
			No CPR witness	304	41
Jabre	IES >30	1 year	Adult relatives of CPA		
			CPR witness	198	20
			No CPR witness	210	32
Zimmerli	?	?	Adult relatives of CPA	101	40
Ingles	IES-R >25	0.5–10 years	Adults relative ≤45 years of CPA	103	44
Present	IES-R >25	30 days	Adult relatives of CPA	54	9

?, not reported; CPA, out-of-hospital cardiac arrest patient; CPR, cardiopulmonary resuscitation; IES, Impact of Event Scale; IES-R, Impact of Event Scale – Revised.

our intervention reduced the frequency of PTSD in bereaved relatives.

Factors associated with increased susceptibility to PTSD include female sex, childhood trauma, fewer years of schooling, prior mental disorders, exposure to four or more traumatic events, deceased being a spouse or child, suicide, a history of exposure to interpersonal violence, bodily disfigurement, traumatic brain injury, and a traumatic experience that is unexpected, inescapable, or uncontrollable.^{1,23–25} Accordingly, most our results of risk factor of high score of the IES-R were compatible with previous reports. However, the present study is the first to show that death inquests tended to be associated with high IES-R score. During death inquests, bereaved relatives are questioned by police to determine the possibility of crime. Even if the relatives were in a stable psychiatric state, being treated as a suspect or reviewing traumatic events could adversely affect their mental status.

In the present study, none of the bereaved family members visited psychiatric medical facilities. In some cases in the present study, however, the assessment of their mental status by a health-care professional might have reduced the individual's potential risk for PTSD. When the health-care professional undertook the screening to identify bereaved family members at risk for PTSD, they also assessed the subject's empathy and concern, their desire to die in order to relieve excruciating pain, and their severe mental anguish or major depression, and offered a helping hand or reassured the bereaved family members they could overcome the issues.¹⁹ Again, given that the effects of our intervention were not investigated in a randomized manner, the results are merely suggestive.

The present study did not show any significant predictors of PTSD based on the findings of a multivariate

analysis. This was because the number of samples was too small. The number of patients with PTSD was only 5, and the model was clearly overfitted. To undertake logistic regression, we used the forced entry procedure using all of the variables, of which there were 12. Ideally, the 12 variables needed 10 times the number of samples for logistic regression, that is, 120 subjects with PTSD.²⁶ This resulted in an extremely unbalanced number of samples between the objective and explanatory variables, thus producing unstable results after statistical calculations in the present study.

The present study is associated with several limitations, including the small number of patients in the study population, approximately half of the bereaved relatives did not consent to participate among all out-of-hospital cardiac arrest patients, and did not use a randomized control method when the pamphlet was distributed to subjects. In addition, we could not provide psychiatric treatment for the bereaved relatives with PTSD because none of the relatives wished to do so. Furthermore, the possibility that the excluded relatives, who did not give their permission to be included in this study, might have PTSD could not be denied. Future studies involving a larger number of patients and a randomized control method are therefore needed to further examine this issue.

CONCLUSION

THE PRESENT STUDY showed that there was 9.3% of Japanese relatives of sudden death victims had PTSD 1 month following the bereavement. The relatives were given a pamphlet that explains the grief process. This frequency was minimal compared to previous reports.

ACKNOWLEDGEMENTS

THIS WORK RECEIVED funding from Ministry of Education, Culture, Sports, Science and Technology (MEXT) – Supported Program for the Strategic Research Foundation at Private Universities, 2015–2019.

DISCLOSURE

Approval of the research protocol: This prospective study protocol was approved by the review board of Juntendo Shizuoka Hospital (approval number: 446).

Informed Consent: We obtained informed consent from all participants.

Registry and the Registration No. of the study/Trial: UMIN Clinical Trials Registry (approval number: UMIN000028128).

Animal Studies: N/A.

Conflict of Interest: We do not have conflict of interest to declare.

REFERENCES

- Shalev A, Liberzon I, Marmar C. Post-traumatic stress disorder. *N. Engl. J. Med.* 2017; 376: 2459–69.
- Jorge RE. 3 Behavioral neurology and neuropsychiatry. *Continuum (Minneapolis, Minn.)*. 2015; 21: 789–805.
- Zisook S, Iglewicz A, Avanzino J *et al.* Bereavement: course, consequences, and care. *Curr. Psychiatry Rep.* 2014; 16: 482.
- Zimmerli M, Tisljar K, Balestra GM, Langewitz W, Marsch S, Hunziker S. Prevalence and risk factors for post-traumatic stress disorder in relatives of out-of-hospital cardiac arrest patients. *Resuscitation.* 2014; 85: 801–8.
- Weiss DS, Marmar CR. The impact of event scale-revised. In: Wilson JP, Keane TM (eds). *Assessing psychological trauma and PTSD*. New York: Guilford Press; 1997:399–411.
- Hyland P, Brewin CR, Maercker A. Predictive validity of ICD-11 PTSD as measured by the impact of event scale-revised: a 15-year prospective study of political prisoners. *J. Trauma Stress.* 2017; 30: 125–32.
- Kazlauskienė J, Bulotienė G. Prevalence of post-traumatic stress disorder among Lithuanian breast cancer patients and its risk factors. *J. Psychosom Res.* 2020; 131: 109939.
- Kim SJ, Yeo JH. Factors affecting posttraumatic stress disorder in south Korean trauma nurses. *J. Trauma. Nurs.* 2020; 27: 50–7.
- Kragh AR, Folke F, Andelius L, Ries ES, Rasmussen RV, Hansen CM. Evaluation of tools to assess psychological distress: how to measure psychological stress reactions in citizen responders- a systematic review. *BMC Emerg. Med.* 2019; 19: 64.
- Nagasawa H, Ishikawa K, Takeuchi I *et al.* The clinical profile of patients with cardiac arrest induced by hemorrhagic stroke. *Resuscitation.* 2017; 120: e5.
- Jitsuiki K, Ishikawa K, Nagasawa H *et al.* Clinical profile of patients with cardiac arrest induced by aortic disease. *Resuscitation.* 2017; 120: e1.
- Ajiki W, Fukunaga T, Saijoh K, Sumino K. Recent status of the medical examiner system in Japan: demographic variation of medicolegal deaths in hyogo prefecture and uncertainty in medicolegal investigations conducted by medical practitioners. *Forensic. Sci. Int.* 1991; 51: 35–50.
- Naber D, Bullinger M. Psychiatric sequelae of cardiac arrest. *Dialogues Clin. Neurosci.* 2018; 20: 73–7.
- Presciutti A, Verma J, Pavol M *et al.* Posttraumatic stress and depressive symptoms characterize cardiac arrest survivors' perceived recovery at hospital discharge. *Gen. Hosp. Psychiatry.* 2018; 53: 108–13.
- Ford J, Rosman L, Wuensch K, Irvine J, Sears SF. Cognitive-behavioral treatment of posttraumatic stress in patients with implantable cardioverter defibrillators: results from a randomized controlled trial. *J. Trauma Stress.* 2016; 29: 388–92.
- Rosman L, Ford J, Whited A *et al.* Compound risk: history of traumatic stress predicts posttraumatic stress disorder symptoms and severity in sudden cardiac arrest survivors. *Eur J Cardiovasc Nurs.* 2016; 15: 372–9.
- Jabre P, Belpomme V, Azoulay E *et al.* Family presence during cardiopulmonary resuscitation. *N. Engl. J. Med.* 2013; 368: 1008–18.
- Jabre P, Tazarourte K, Azoulay E *et al.* Offering the opportunity for family to be present during cardiopulmonary resuscitation: 1-year assessment. *Intensive Care Med.* 2014; 40: 981–7.
- Compton S, Grace H, Madgy A, Swor RA. Post-traumatic stress disorder symptomology associated with witnessing unsuccessful out-of-hospital cardiopulmonary resuscitation. *Acad Emerg Med.* 2009; 16: 226–9.
- Ingles J, Spinks C, Yeates L, McGeechan K, Kasparian N, Semsarian C. Posttraumatic stress and prolonged grief after the sudden cardiac death of a young relative. *JAMA Intern. Med.* 2016; 176: 402–5.
- Morina N, Wicherts JM, Lobbrecht J, Priebe S. Remission from post-traumatic stress disorder in adults: a systematic review and meta-analysis of long term outcome studies. *Clin Psychol Rev.* 2014; 34: 249–55.
- Whealin JM, Nelson D, Stotzer R, Guerrero A, Carpenter M, Pietrzak RH. Risk and resilience factors associated with posttraumatic stress in ethno-racially diverse National Guard members in Hawai'i. *Psychiatry Res.* 2015; 227: 270–7.
- Atwoli L, Stein DJ, King A *et al.* Posttraumatic stress disorder associated with unexpected death of a loved one: cross-national findings from the world mental health surveys. *Depress Anxiety.* 2017; 34(4): 315–26.

- 24 Mitchell AM, Terhorst L. PTSD symptoms in survivors bereaved by the suicide of a significant other. *J. Am. Psychiatr. Nurses Assoc.* 2017; 23: 61–5.
- 25 O'Rourke MC, Jamil RT, Siddiqui W. (eds). Suicide screening and prevention. In: StatPearls [Internet]. Florida: StatPearls, Treasure Island; 2020. [cited 13 July 2020]. <https://pubmed.ncbi.nlm.nih.gov/30285348/>.
- 26 Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *J. Clin. Epidemiol.* 1996; 49: 1373–9.