Journal of Critical Care 53 (2019) 231–235

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Quality of life assessment following amputation for septic shock: a long-term descriptive survey after symmetric peripheral gangrene

Pierre Labroca, MD [a], Gérard Chiesa, MD [b], Isabelle Laroyenne, MD [c], Léo Borrini, MD [d], Rémi Klotz, MD [e], Quoc Phan Sy, MD [f], Marie-Christine Cristina, MD [g], Anne Brunon Martinez, MD [h], Pierre-Edouard Bollaert, MD, PhD [a], Jean Paysant, MD, PhD [i], Jérémie Lemarié, MD, PhD [a,*]

[a] Réanimation médicale, hôpital central, C.H.R.U. de Nancy, Nancy, France
[b] Service de rééducation et d'appareillage, Institut Robert Merle d'Aubigné, Valenton, France
[c] Service de médecine physique et de réadaptation, Centre Médico-Chirurgical de Réadaptation des Massues, Lyon, France
[d] Service de médecine physique et de réadaptation, Hôpital d'Instruction des Armées Percy, Clamart, France
[e] Service de médecine physique et de réadaptation, centre de médecine physique et de réadaptation de la tour de Gassies, Bruges, France
[f] Service de médecine physique et de réadaptation, Hôpital la renaissance sanitaire, Villiers-Saint-Denis, France
[g] Service de médecine physique et de réadaptation, Pôle Saint Hélier, Rennes, France
[h] Service de rééducation réadaptation, Hôpital Universitaire du Grau du Roi, Le Grau du Roi, France
[i] Centre Louis Pierquin, Institut Régional de Médecine Physique et de Réadaptation, Nancy, France

ARTICLE INFO

Keywords:
Septic shock
Ethics
HRQOL

ABSTRACT

Purpose: To assess health-related quality of life (HRQOL) following rehabilitation of amputees suffering symmetric peripheral gangrene (SPG) after septic shock.
Material and methods: A retrospective cohort study was conducted in nine French specialized rehabilitation centers. Thirty-two ICU adult patients hospitalized between 2005 and 2015 for septic shock who additionally presented with SPG resulting in at least two major amputations were enrolled. HRQOL was assessed by EQ-5D-3 L questionnaire.
Results: All patients (mean ICU length of stay 39 ± 22d, SAPS II 58 ± 18) had both lower limbs amputated and 84% were quadruple amputees. HRQOL, assessed 4.8 ± 2.8 years after amputation, was inferior to the French reference. However, patients' self-rated health status was similar to the reference at the time of HRQOL assessment. The main factor of impaired HRQOL was intense phantom pain, not the mobility or self-care dimensions of EQ-5D. All patients except one preferred to be treated again for SPG despite disability.
Conclusion: ICU survivors referred to rehabilitation centers after SPG-related amputations had impaired HRQOL. At the time of HRQOL assessment, they considered themselves in good health and preferred to be treated again despite disability. Appraisal of long-term functional outcome should not be used to guide end-of-life decision-making in this situation.

1. Introduction

Symmetric peripheral gangrene (SPG) is a serious but very rare complication of septic shock. SPG elicits acral necrosis (more frequently in the distal limbs), while *purpura fulminans* relates to extensive, multicentric, non-acral skin necrosis. Both syndromes are generally mixed. In the 1920's, Shwartzman was the first to report their pathological features: microthrombi, endothelial cell swelling and necrotizing neutrophilic vasculitis [1]. However, a century later, understanding of the pathophysiology is still limited. Currently, the epidemiology of SPG is poorly understood. One to four-limb amputation is the most frequent outcome of SPG with reported rates of amputation around 90% [2-4]. Disability can be limited by limb prostheses and several teams have reported successful rehabilitation and independent functioning, even in quadruple amputees [5-8]. Recent data suggests impairment in health-related quality of life (HRQOL) after critical illness and its assessment should always be of paramount interest to patient-centered care [9]. Besides, physician's self-perception of disability may lead to inappropriate decision to withdraw or withhold life-sustaining therapies.

Abbreviations: HRQOL, health-related quality of life; SD, standard deviation; SPG, symmetric peripheral gangrene; VAS, Visual Analogue Scale.

* Corresponding author at: Service de Réanimation médicale, Hôpital Central, Centre Hospitalier Universitaire Régional de Nancy, 29 avenue du Maréchal de Lattre de Tassigny, 54000 Nancy, France.
E-mail address: j.lemarie@chru-nancy.fr (J. Lemarié).

https://doi.org/10.1016/j.jcrc.2019.06.027
0883-9441/

In this context, our main objective was to assess HRQOL of adult amputees after severe SPG once rehabilitation was achieved, using a validated and standardized instrument.

2. Methods

2.1. Study design

There are few specialized tertiary rehabilitation referral centers for amputees in France (one major rehabilitation center in each region, except around Paris). We conducted a retrospective multicenter study by contacting every referring physician for amputees in each of these referral centers to identify eligible patients from January 1, 2005 to December 31, 2015. Eligible patients were adults (18 years old or older) who had undergone two to four-limb amputations related to SPG and required discharge to a specialized rehabilitation center after ICU hospitalization for septic shock. When included, patients had to be using their final limb prostheses. Exclusion criteria comprised of inability to understand French, amputation of isolated phalanx or toes, one-limb amputation after necrotizing fasciitis, as well as limb amputations with strong evidence for an underlying cause for limb ischemia (especially preexisting vascular disease or arterial embolism). The referring physicians were responsible for screening patients (search by keywords in their patients' database) and for obtaining agreements from eligible patients. Following which, investigators mailed an information letter and a consent form. If patients mailed back their signed consent form, a unique investigator (P.L.) contacted them to administer the questionnaire. The phone call was semi-directive and lasted for about thirty minutes. The protocol was approved by the French Intensive Care Society's ethical committee.

2.2. Clinical data collection

The following data from ICU hospitalization reports were collected: length of ICU stay, infectious agent, site of infection, data regarding organ dysfunction (acute kidney injury according to the KDIGO definition [10], disseminated intravascular coagulopathy according to the ISRH scoring system [11] and acute liver failure (as stated in the hospitalization report)) and data regarding the use of supportive therapies (vasopressor, mechanical ventilation, renal replacement therapy). The Charlson comorbidity index was calculated and collected. Amputations were characterized minor or major as follows. Regarding upper limbs, an amputation was considered minor when only phalanx or fingers were removed with respect of the metacarpus, otherwise it was considered major. Regarding lower limbs, an amputation was considered minor from toes to transmetatarsal amputations, otherwise it was considered major.

2.3. Questionnaire

HRQOL was assessed by EQ-5D-3 L (EuroQol Research Foundation, Rotterdam, The Netherlands) [12]. The EQ5D questionnaire consists of five questions (primary dimensions) about mobility, self-care, usual activities, pain/ discomfort, and anxiety/depression, which all have three possible answers (level 1 “no problems”, level 2 “some problems”, level 3 “extreme problems”). For each patient, an index of HRQOL (EQ-5D index) is calculated with respect to the national population coefficients (each country has a different formula). This EQ-5D index indicates the preference of being in a certain health state and each country has its own norms and values for these health states. Additionally, EQ-5D includes self-reported overall quality of life as a linear 100-point scale, the Visual Analogue Scale (VAS), where 0 is the worst imaginable health state and 100 is the best imaginable health state. Patients were invited to rate their current VAS. We also asked the patients to rate their global health state before SPG using this VAS. To better explore the pain/discomfort and anxiety/depression dimensions, we collected data regarding the use of analgesics, anxiolytics and antidepressant agents at the time of interview.

Patients of working age were asked to answer questions one and five of the Work Ability Index: (i) *current work ability compared with the lifetime* assessed by a visual analogue scale rated from 0 to 10 and (ii) *own prognosis of work ability two years from now* with three answers (unlikely, uncertain, relatively certain) [13].

Home environment was evaluated using the “CONSTANCES” population-based French epidemiological survey, which explores marital status (question 76) and the number of people living at home (question 77) [14]. Patients were asked if they thought they had strong support and helpful close circle (relatives and friends).

Finally, we asked patients if they would be willing to be treated again for symmetric peripheral gangrene.

2.4. Statistical analysis

Continuous data are reported as mean ± standard deviation (SD) and categorical data are reported as frequencies and percentages. The association between HRQOL variables was evaluated by use of a Pearson correlation analysis. Between-group differences were assessed by Chi-square test for categorical data. All statistical tests were two-sided, and a p value $<.05$ was considered to indicate statistical significance.

3. Results

3.1. Population

In 2016, 13 tertiary rehabilitation centers were contacted, out of which nine agreed to participate. Sixty-one eligible patients were identified. Each center identified between 2 and 5 patients. One center (Institut Robert Merle, Valenton, France) identified 31 eligible patients. Among the 61 eligible patients, one was dead at the time of the study, two withheld participation and 26 were lost to follow up (24 wrong mail addresses and no contact with the rehabilitation center for months or years, 2 consent forms never mailed back despite dunning letters; most of these patients were from foreign countries). Thirty-two patients consented to participate and were phoned for questionnaire administration in 2017, while 29 ICU reports were available (Fig. 1).

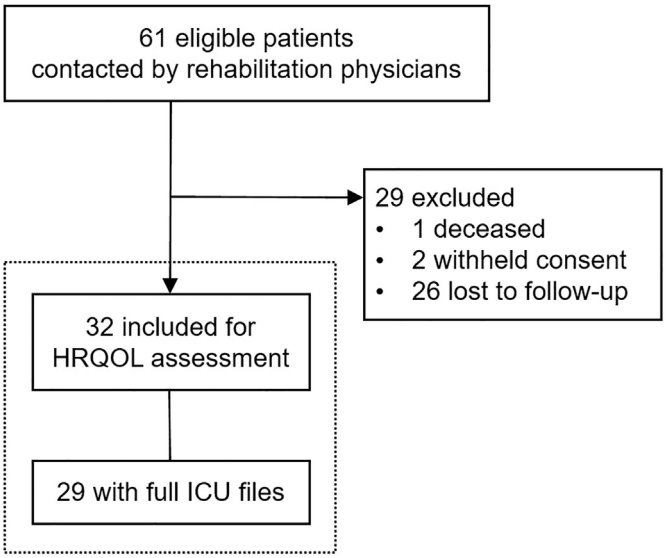

Fig. 1. Flow chart of included patients.

3.2. Patients' characteristics during ICU hospitalization

Demographic and medical features at the onset of the critical illness were available for 29 patients and are detailed in Table 1. Specific data about organ failures and supportive therapies were available for 27/29 patients from the ICU hospitalization reports. All of them except one were mechanically ventilated, all received vasopressors, and all had acute kidney injury, of whom 78% underwent renal replacement therapy. One patient required veno-arterial extra-corporeal membrane oxygenation. Disseminated intravascular coagulation was reported for 24 (89%) patients while data were missing for the three remaining patients. Thrombocytopenia was lower than 20 G/L in fifteen (56%) patients. Five patients (15%) had acquired immunosuppressive comorbidities: HIV without AIDS ($n = 2$), splenectomy ($n = 1$), immunosuppressive therapy ($n = 2$). Full list of comorbidities is available in Table 2.

A microorganism was identified in 27/29 (84%) ICU reports which detailed culture findings. *Streptococcus* species (P*neumococcus* and group A *Streptococcus*) were the main responsible microorganisms (10/29, 34%), followed by *Neisseria meningitidis* (7/29, 24%), *Escherichia coli* (5/29, 17%) and *Staphylococcus* species (3/29, 10%). The main sites of infection were meninges (10/29, 34%), lung (6/29, 21%), urinary tract (5/29, 17%) and skin and soft tissues (3/29, 10%).

3.3. HRQOL

The questionnaire was administered to 32 patients (19/13, f/m), aged 57 (±17) years old. HRQOL was evaluated after a mean follow-up of 4.8 ± 2.8 years (time from ICU discharge). All patients lived at home and a majority of them ($n = 19$, 59%,) lived with a partner. All patients but one (who lived alone) qualified their social and family environment as excellent (*i.e.* easily available for any help). Eighteen (56%) had home-based services (private duty nurse and/or assistant nurse and/or maid).

All patients had both lower limbs amputated. Four of them (13%) had no >2 limbs amputated, 1 (3%) had 3 and 27 (84%) had 4 limbs amputation. Regarding upper limbs, 6 (19%) patients had two major amputations and 3 (9%) had one major amputation. The main lower limb amputation level was transtibial; only one patient underwent transfemoral amputation.

Twenty patients (63%) were retired or declared disabled by the French National Health Insurance. Among the 12 remaining patients, 3 (9%) were currently working (one as managing director and two as office clerks), six (18%) hoped they would work in the next two years and 3 (9%) considered that going back to work was unlikely or relatively uncertain.

The EQ-5D index relative to age groups was always lower than the reference for the French population except for patients aged 25–34 years old (Fig. 2). Regarding self-assessment of health state, VAS before gangrene was higher than the French population reference relative to age group, whereas VAS after gangrene tended to be equal or lower to the reference (Fig. 3). When comparing the before-after difference within the study population, VAS rating was significantly lower after gangrene ($\Delta VAS = -22 \pm 23$ $p < .01$). Correlation was weak between values of current VAS and EQ index ($R = 0.43$, $p < 0{,}05$).

The number of "some problems" and "extreme problems" ratings increased with ageing, as observed in the general population (e-Table 1). However, despite lower limbs amputations, no patient reported being bedridden. Seventeen patients (53%) had some problems in their usual activities and 10 (31%) in self-care. Anxiety or depression were graded "no problems" by 21 (66%) and "extreme problems" by only 2 patients. Among the total 160 rating values, 18 (11%) were "extreme problems" and half of these ratings were related to "pain/discomfort". Fifteen patients (47%) chronically used analgesics; among them 8 (25%) also used anxiolytics/antidepressants. There was a statistically significant association between the use of analgesics and anxiolytics/antidepressants ($p = .006$). Fourteen (44%) used neither painkillers nor anxiolytic/antidepressants.

Patients were finally asked if they willed to be treated again for SPG. All but one answered yes (31/32, 97%).

Table 1
Demographic data, severity of illness and organ failures of the study population.

Variable	Value
Age, years	53 ± 17[a]
Charlson comorbidity Index	2 ± 2[a]
ICU length of stay, days	39 ± 22[a]
Simplified Acute Physiology Score II	58 ± 18[a]
Invasive Mechanical Ventilation (n, yes/no/missing data)	26/1/5
Vasopressors (n, yes/no/missing data)	27/0/5
Renal Replacement Therapy for acute kidney injury (n, yes/no/missing data)	21/6/5
Liver Dysfunction (n, yes/no/missing data)	9/18/5
Disseminated Intravascular Coagulation (n, yes/no/missing data)	24/0/8

Mean ± standard deviation; ICU: Intensive care unit.
[a] Refers to 29 patients with ICU hospitalization report available.

Table 2
Associated comorbidities at the onset of SPG.

Comorbidity	Number (%), $N = 32$
None	8 (25%)
Hypertension	8 (25%)
HIV (without AIDS)	2 (6%)
Autoimmune disorder	4 (12%)
Solid cancer in remission	5 (15%)
Hematologic malignancies in remission	2 (6%)
Immunosuppressive therapy	2 (6%)
Chronic heart failure	4 (12%)
COPD	2 (6%)
Diabetes	1 (3%)

HIV: Human immunodeficiency virus, AIDS: acquired immune deficiency syndrome, COPD: chronic obstructive pulmonary disease.

4. Discussion

Herein we provide the results of the largest study aiming to evaluate long-term HRQOL in adult amputees who survived sepsis-induced SPG. We used a validated and standardized instrument. Our main findings are: (i) SPG survivors reported impaired HRQOL compared to the French

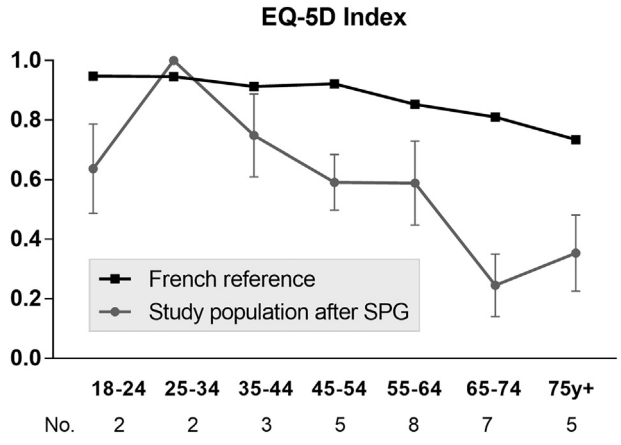

Fig. 2. Health-related quality of life assessment by the EQ-5D index and comparison with the French reference population. EQ-5D index was calculated by questionnaire-based survey after SPG. For each patient, five primary dimensions (mobility, self-care, usual activities, pain/ discomfort, and anxiety/depression) were explored and graded. No: number of patients.

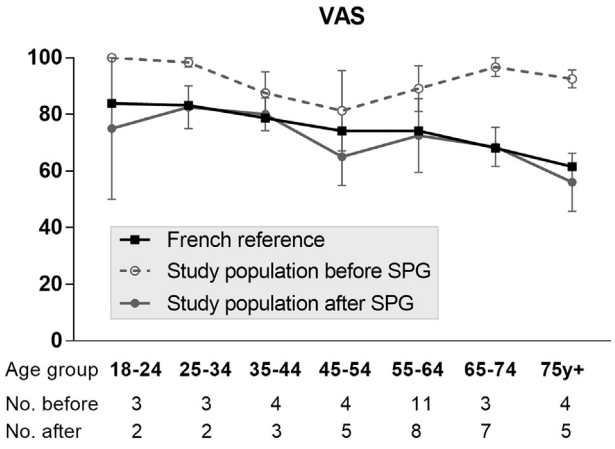

Fig. 3. Health-related quality of life assessment by VAS and comparison with the French reference population. Self-assessment of HRQOL by visual analogue scale (VAS) (ratings from 0 to 100, representing the worst and the best imaginable health states respectively) before and after the SPG in the study population and comparison with the French population, by age-groups. No: number of patients; SPG: symmetric peripheral gangrene.

reference population, (ii) pain was the main driver of HRQOL impairment, (iii) no patient reported being bedridden and (iv) all but one willed to be treated again despite disability.

Last year, another large French multicenter cohort of *purpura fulminans* patients (*i.e.* the HOPEFUL study) identified 306 patients, of whom 180 survived during the follow-up period. Fifty-one (28%) were amputated and the authors were able to evaluate HRQOL in 12 of these *purpura fulminans*-related amputated patients [15,16].

However, the question of the acceptability of performing disabling limb amputations was not part of their questionnaire. We asked this question and 97% of the patients answered that they would be willing to be treated again for SPG rather than death. Such observation strongly argues for very cautious withdrawal of life-sustaining therapies and therapeutic limitation based on self-perception of disability. As 4 patients (13%) were over 75 years-old, this could remain true even in elderly patients. However, as displayed in Fig. 2, the decline in EQ-5D index seemed to be more pronounced in older patients than in younger patients, as illustrated by a larger deviation from the reference population for the last two groups (over 65 years old).

Our patients reported a severe impairment of HRQOL, as illustrated by lower EQ-5D index values than the reference population in each age group but one. Using another questionnaire (*i.e.* SF-36), the HOPEFUL investigators also found such a decrease in *purpura fulminans* patients, whether amputated or not, when compared to the general population [15]. HRQOL almost always decreases after critical care [9,17]. However, based on VAS scores after SPG, they favorably rated their own health state, which could illustrate how they coped with their disability. In our study, the mean decrease in VAS was 22 (±23). By contrast, in patients with severe sepsis a mean decrease of 8 was previously reported [18]. The general ICU population often has pre-existing diseases and a pre-existing low HRQOL [19-21]. The suddenness of acute illness in patients without chronic disease could explain the drop in VAS we observed. However, as patients *a posteriori* self-estimated their HRQOL prior to SPG, there is an obvious bias of memorization which could lead to an overestimation of their baseline VAS.

Lastly, when looking at each dimension of EQ-5D-3 L, we observed that no patient was bedridden despite multiple amputations. This observation was also reported by the HOPEFUL investigators [15]. Unexpectedly, most "extreme" problems (level 3) were rated in the pain/discomfort dimension (9 (28%) patients) rather than in the self-care or mobility dimensions. Applying general population rates to the study population, only one patient would have declared extreme pain/discomfort. Significant association between analgesics and antidepressants use emphasizes the intensity of pain in the study population. Phantom pain and prostheses-related pain are well-known symptoms and a better treatment could improve HRQOL [22-24]. Of note, more pain was also observed between amputated and non-amputated patients enrolled in the HOPEFUL study [15].

Our cohort may inaccurately reflect the epidemiology of SPG. First, we selected severely disabled patients, as two or more limb amputations were required for inclusion. Recruiting patients from tertiary rehabilitation centers likely resulted in the inclusion of the most severe patients only. >80% had 4-limb amputation, which is higher than previous reports. For instance, in their mainly pediatric multicenter study focusing on *purpura fulminans,* Warner *et al* observed 26% of quadruple amputation [4], while Contou et al. reported a median of 3 amputations [16]. Second, half of eligible patients were lost to follow up. We could hypothesize that some of these patients could have express poorer HRQOL or opposite opinions about being treated again for SPG. Third, in the absence of a dedicated network of rehabilitation centers, some eligible patients may have been sent to other hospitals. Last, there was a bias of memorization because referring physicians screened patients. In the absence of a specific entry for SPG in the French Health Coding System and because of the small proportion of SPG patients among all the amputated patients referred to these rehabilitation centers, the referring physicians identified the most recent patients more easily. Indeed, two thirds of the patients were hospitalized after 2010 (*i.e.* during the second half of the inclusion period). Such an increase in the incidence of SPG is unlikely.

5. Conclusion

SPG is a rare complication of septic shock. While keeping in mind the limitations inherent to the retrospective design, we showed that survivors discharged home after rehabilitation had impaired survey-based HRQOL while they favorably evaluated their own health state. Residual pain played a detrimental role in HRQOL. It is likely that pain management strategies could further improve HRQOL in this specific population. Despite multiple amputations, survivors retrospectively willed to be treated again. Before withdrawing life-sustaining therapies in such situations that one could no longer consider worth living, intensivists should remember that the appraisal of bad or good outcome based on forthcoming disability may not reflect the patient's future satisfaction and HRQOL.

Financial disclosure statement

No financial support was received for this study. No financial disclosures are declared by any of the authors.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2019.06.027.

References

[1] Shwartzman G. Studies on Bacillus Typhosus toxic substances : I. phenomenon of local skin reactivity to B. Typhosus culture filtrate. J Exp Med 1928 Jul 31;48(2):247–68.

[2] Bache CE, Torode IP. Orthopaedic sequelae of meningococcal septicemia. J Pediatr Orthop 2006 Feb;26(1):135–9.
[3] Buysse CMP, Oranje AP, Zuidema E, Hazelzet JA, Hop WCJ, Diepstraten AF, et al. Long-term skin scarring and orthopaedic sequelae in survivors of meningococcal septic shock. Arch Dis Child 2009 May;94(5):381–6.
[4] Warner PM, Kagan RJ, Yakuboff KP, Kemalyan N, Palmieri TL, Greenhalgh DG, et al. Current management of purpura fulminans: a multicenter study. J Burn Care Rehabil 2003 Jun;24(3):119–26.
[5] Shin JC, Yang HE, Yu SJ, Kim NY, Yoon SY. Stepwise rehabilitation of the triple amputee combined with dysfunction of the sound limb. Ann Rehabil Med 2014 Feb;38(1):116–21.
[6] Yoshimoto K, Okuma Y, Nakamura T, Mita T, Mitsumoto A, Yamasaki N, et al. Limb fitting for quadruple amputees: report of two cases of symmetrical peripheral gangrene caused by pneumococcal purpura fulminans. Prosthetics Orthot Int 2013 Dec;37(6):489–94.
[7] Hacking HG, Lo-a-Njoe BA, Visser-Meily JM. Multiple amputations due to sepsis: however, functional rehabilitation is possible. Ned Tijdschr Geneeskd 1999 May 22;143(21):1073–7.
[8] Lowe KG, Boyce JM. Rehabilitation of a child with meningococcal septicemia and quadrilateral limb loss: a case report. Arch Phys Med Rehabil 2004 Aug;85(8):1354–7.
[9] Oeyen SG, Vandijck DM, Benoit DD, Annemans L, Decruyenaere JM. Quality of life after intensive care: a systematic review of the literature. Crit Care Med 2010 Dec;38(12):2386–400.
[10] Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 2012;120(4):c179–84.
[11] Lee JH, Song JW, Song KS. Diagnosis of overt disseminated intravascular coagulation: a comparative study using criteria from the international society versus the Korean Society on Thrombosis and Hemostasis. Yonsei Med J 2007 Aug 31;48(4):595–600.
[12] Cabasés J, Rabin R. Introduction. In: Szende A, Janssen B, Cabases J, editors. Self-reported population health: An international perspective based on EQ-5D [internet]. Dordrecht: Springer; 2014 Available from: http://www.ncbi.nlm.nih.gov/books/NBK500360/.
[13] llmarinen J. The work ability index (WAI). Occup Med 2007 Mar 1;57(2) 160–160.
[14] Constances | Améliorer la santé de demain. Available from: http://www.constances.fr/index_EN.php.
[15] Contou D, Canoui-Poitrine F, Coudroy R, Préau S, Cour M, Barbier F, et al. Long-term quality of life in adult patients surviving purpura fulminans: an exposed-unexposed multicenter cohort study. Clin Infect Dis 2018 Oct 16. https://doi.org/10.1093/cid/ciy901 [Epub ahead of print].
[16] Contou D, Sonneville R, Canoui-Poitrine F, Colin G, Coudroy R, Pène F, et al. Clinical spectrum and short-term outcome of adult patients with purpura fulminans: a French multicenter retrospective cohort study. Intensive Care Med 2018 Sep;44(9):1502–11.
[17] Cuthbertson BH, Elders A, Hall S, Taylor J, MacLennan G, Mackirdy F, et al. Mortality and quality of life in the five years after severe sepsis. Crit Care 2013;17(2):R70.
[18] Karlsson S, Ruokonen E, Varpula T, Ala-Kokko TI, Pettilä V, Finnsepsis Study Group. Long-term outcome and quality-adjusted life years after severe sepsis. Crit Care Med 2009 Apr;37(4):1268–74.
[19] Soliman IW, de Lange DW, Peelen LM, Cremer OL, Slooter AJC, Pasma W, et al. Single-center large-cohort study into quality of life in Dutch intensive care unit subgroups, 1 year after admission, using EuroQoL EQ-6D-3L. J Crit Care 2015 Feb;30(1):181–6.
[20] Orwelius L, Nordlund A, Nordlund P, Simonsson E, Bäckman C, Samuelsson A, et al. Pre-existing disease: the most important factor for health related quality of life long-term after critical illness: a prospective, longitudinal, multicentre trial. Crit Care Lond Engl 2010;14(2):R67.
[21] Hofhuis JGM, Spronk PE, van Stel HF, Schrijvers GJP, Rommes JH, Bakker J. The impact of critical illness on perceived health-related quality of life during ICU treatment, hospital stay, and after hospital discharge: a long-term follow-up study. Chest 2008 Feb;133(2):377–85.
[22] Nikolajsen L. Postamputation pain: studies on mechanisms. Dan Med J 2012 Oct;59(10):B4527.
[23] Hsu E, Cohen SP. Postamputation pain: epidemiology, mechanisms, and treatment. J Pain Res 2013 Feb 13;6:121–36.
[24] Uustal H, Meier RH. Pain issues and treatment of the person with an amputation. Phys Med Rehabil Clin N Am 2014 Feb;25(1):45–52.