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Posted Date: 19 December 2023

doi: 10.20944/preprints202312.1452.v1

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Article

Epidemiological Data, Functional Outcome, and Quality of Life of Patients with Multiple Amputations Due to Septic Shock

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Abstract: 1. Background: Septic shock is a rare and serious infectious disease. Patients surviving the early phase are at high risk of multiple amputations of limbs. They are potential sources of serious disability. 2. Methods: The objective was to describe the functional prognosis and quality of life of the four-limb amputee patients following septic shock. This is a descriptive, retrospective and mono-centric study. The patients included between 2010 and 2019 had septic shock after 18 years, responsible for amputation of the four limbs. We studied the mean age of septic shock, the causative organisms, the infectious door enter, the different levels of amputation, the fitting process, the resumption of walking, the Functional Independence Measure (FIM) and the SF-12 Quality of Life Questionnaire. 3. Results: We suceed to include 15 patients.. 53.3% women and 46.7% men with an average age of 46.1 years. 80% presented bilateral trans-tibial amputations, all were able to return walking even over short distances, within an average of 8.4 months. 40% did not require a technical walking aid, 33.3% had no walking perimeter limitation. 47% had a higher mental and social quality of life score than the general population. The younger the patients, the better their physical quality of life. After two years of follow-up, the younger the patients, the better their functional autonomy. Patients with better functional autonomy had a better physical quality of life. 4. Conclusion: The number of amputations due to spetic shock is likely to increase in the years to come throughout the world. Our study prove that quadri-amputee patient can regain a fully acceptable functional and quality of life being monitored in a specialized health center with multidisciplinary health professional to help him.

Keywords: QOL; septic choc; quadri-amputation; epidemiological data

1. Introduction

An estimated 70 000 cases of severe sepsis occur in France per year and this issue is the first cause of mortality in intensive care units (1). Patients who survive the early stages of septic shock are at high risk of severe complications linked with acute cutaneous necrosis or Symmetrical Peripheral Gangrene (SPG), caused either by Disseminated Intravascular Coagulation (DIC) or the use of an inotropic agent. Deep muscle damage, skin lesions, ischemia-related bone and cartilage lesions can be widespread and simultaneously affect the extremities of the four limbs. This can lead to multiple amputations, or even quadrilateral limb loss, to remove body parts which engage the functional prognosis (2).

Nearly 30% of survivors of Purpura Fulminans (PF) have one or several amputated limbs (3). SPG is also associated with a high rate of multiple limb amputations in 70% to 90% of surviving patients (4,5). Although the clinical characteristics and consequences of septic shock and of PF have been well studied in paediatric populations (6–10), only few data are available for adult patients and these are often limited to the field of intensive care (11) and the subsequent care of patients. Indeed, data in the literature on the fate of these patients in the years following the acute episode are lacking (12) or limited to a few case reports (10,13,14). However, the prevalence rate of septic shocks seems

 doi:10.20944/preprints202312.1452.v1

to increase in the general population, though the survival of patients increases as well, thanks to advances in intensive care (15).

Injuries resulting from septic shock, especially multiple amputations, cause severe disability (14). This disability can be limited thanks to rehabilitative care and suitable prostheses. Several teams reported a good functional assessment in quadruple amputees (10,16–18).

Change in quality of life related to health, after a serious disease, and its evaluation is an inherent part of the field of Physical Medicine and Rehabilitation (PMR) (19).

Furthermore, we hypothesize that the intensive care physician's self-perception of disability, who does not have a functional view, can lead to cessation of care. In this context, our main objective was to assess the quality of life and functional outcome of adult amputees after septic shock, after their rehabilitation with validated and standardized instruments.

2. Materials and Methods

This descriptive, retrospective and monocentric study was conducted at the Institute Robert Merle d'Aubigné, a functional rehabilitation and prosthetics center in Valenton, France (Ile-de-France - 94).

The list of patients was obtained with the code CIM-10: R572 Septic shock, D65 Disseminated Intravascular Coagulation, D692 Other purpura (nonthrombocytopenic) and/or Z898 Surgical amputation of both upper and lower limbs [any level]. The inclusion criteria for patients were:

- A septic shock during adulthood (>18 years)
- A septic shock between 2010 and 2019
- A quadrilateral amputation (upper and lower limbs) at any level of amputation
- Consulting and care at the Institut Robert Merle d'Aubigné
- Prescription of prostheses by a doctor at the Institut Robert Merle d'Aubigné

The data were collected thanks to the computerized medical records of patients. These were then completed with the patients after obtaining their informed consent for their inclusion in this study and informing them about the possibility of withdrawal.

We chose two standardized questionnaires: the Functional Independence Measure (FIM) and the 12-item short-form survey (SF-12) to assess quality of life.

FIM was developed to evaluate independence and functional dependency, and has been extensively validated in scientific literature (20,21). Several studies validated the use of FIM in a population of lower limb amputees (22,23). The tool includes 18 items grouped into five main categories: self-care, mobility/transfers, locomotion, communication and social cognition. It gives a total score for all these items, and a motor subscale and cognition subscale. Several studies (24–26) underline the importance of using the two subscales independently, and their use was already studied in populations of amputees (27).

SF-12 gives two scores: a score of mental and social quality of life, and a score of physical quality of life. These two scores were built in such a way that the average score in the general population is 50. SF-12 can be used for general population surveys or for patient surveys (28).

3. Data Analysis

Qualitative data were described using number and percentage. Quantitative data were described using the mean, standard-deviation, median, minimum and maximum.

Shapiro-Wilk Normality Tests were performed in order to check the distribution of quantitative variables. Only the variables "total FIM score" and "FIM motor score" did not have a normal distribution (p-value < 0,05), and therefore, non-parametric tests (Wilcoxon-Mann-Whitney Test and Kruskal-Wallis Test) were used. For the other variables, parametric tests (Student's T test and ANOVA) were used.

In the absence of an existing score in the literature, we created an empirical score of amputation by awarding points according to the level of amputation for each limb (1: amputation of the toes/fingers, 2: metacarpal/transmetatarsal amputation and 3: transtibial/transradial amputation). In

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the interests of simplicity, wrist disarticulation, carpometacarpal amputation, metacarpophalangeal amputation, transcarpal amputation, were grouped in amputation of the carpus. Thus, the amputation score for each subject ranges between a minimum of 4 and a maximum of 12

In order to study the relationships between each quantitative variable, correlations were estimated by calculating Spearman's correlation coefficient, whose distribution is close to normal, and by representing a parameter correlation matrix. These correlations were calculated according to two subgroups based on the elapsed time after the septic shock (≤24 months and >24 months). Correlations were considered as low, moderate, or strong, at r or ϱ ≥0,3, ≥0,5 and ≥0,7, respectively.

Due to the small population size, it was not possible to perform a multivariate analysis comparing the parameters of interest. In order to consider both quantitative variables (time after amputation and scores) and qualitative variables, such as the elapsed time after septic shock (≤24 months and >24 months) and gender, we performed a latent class analysis. This analysis also allowed us to highlight different types of profiles depending on the characteristics of the subjects. A latent class model can be considered as a probabilistic clustering model (or unsupervised classification). The objective is the same as that of clustering but with a top-down approach: to identify homogenous groups inside a larger population. This model describes data distribution and makes it possible to evaluate the probabilities that certain subjects are members of selected classes. We chose to create a model with two classes.

All the tests are bilateral with a threshold level of 5%. All the analyses were performed with the software R 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria, http://www.r-project.org) and the extension XSLSTAT in Excel.

Statistical data Apply the APA style for presenting statistical data: MEAN (SD) or MEDIAN (Q1; Q3). Do not use ±. Remove decimals for % data. Exact p-values must be given for p > 10-3 in the form stand 0.007. p < 10-3, indicate if it is < 10-3, < 10-4, < 10-6. Main effect size must be given, including for non-parametric statistics. The risk of statistical inflation must be measured by limiting statistical tests to hypothesis formulated, and by adjusting p-values for multiple comparisons.

4. Results

4.1. Epidemiology

Sixty patient medical records were collected thanks to the CIM-10 code. Among the 35 patients referred to our institute after 2010, 25 (71.4%) had four limb amputations. One patient was under the age of 18 (2 years old) at the time of the septic shock, one patient died before the beginning of the study, three patients were lost to follow-up, and five refused to participate in the study.

In total, 15 patients participated in this study.

The mean age at the time of septic shock was 46.1 years [±16.4]. Among the participants, 53.3% were women and 46.7% were men. The mean time between the date of the septic shock and the beginning of the study was 40.3 months [±36.3], or equivalent to 3 years and 4 months.

4.2. Levels of amputation

In the lower limbs: 80% of patients had bilateral transtibial amputations, 13.3% had a unilateral transtibial amputation and a transmetatarsal amputation on the other side, and 6.7% of patients had toe amputations only (phalanx P3 to P1).

In the upper limbs: 13.3% of patients had bilateral transradial amputations, 6.7% had a transradial and transmetacarpal amputation, 33.3% had a bilateral amputation of the carpus*, 13.3% had a transmetacarpal amputation and amputated fingers (P1 to P3), and 33.3% had amputations of the fingers only.

4.3. Prostheses

All patients received prostheses at the lower limbs and were able to resume ambulation. It took patients 8.4 months on average [±6,25] to resume walking after the septic shock.

 doi:10.20944/preprints202312.1452.v1

Forty percent (40%) of patients ambulated with prostheses at the lower limbs without any technical assistance and 20% required a technical assistance (cane or crutch) outdoors. The other 40% ambulated over short distances indoors, but most of the time used wheelchairs. No patients were completely dependent on electric or manual wheelchairs. Among the patients, 33.3% reported an unlimited walking distance, 26.7% walked 1 to 2 hours per day, 33.3% walked between 30 minutes and 1h per day, and 6.7% had a walking distance <30 min (this patient was questioned 1 month after hospital discharge). Furthermore, 67% of patients harnessed their prostheses independently, 66.7% wore their prostheses from morning till evening (>9h/day), 20% wore them 6-7h/day, and 13.3% 3-4h/day.

In the upper limbs, 33% of patients received a prosthesis but 20% did not wear it. In all cases, it was a cosmetic prosthesis for amputations of the fingers or transmetacarpal amputations. Only 2 patients (13%) wore their prosthesis on a daily basis and for most everyday activities. In this case, the patients were fitted with a myoelectric functional prosthesis (Sensor Speed) and displayed high levels of amputation: one had bilateral transradial amputations and the other transradial/transmetatarsal amputations.

Two patients (13%) refused the prescription of prostheses, both had amputations of the fingers only.

Finally, 54% (8 patients) were still awaiting their prostheses at the time of the study.

4.4. Way of life

Among the patients, 33% benefited from a change of residence for persons with reduced mobility (PRM), and 67% did not change residence (27% did not require adaptive equipment and 40% required equipment, or home modifications).

On a professional level, 27% of patients were already retired at the time of the septic shock, 46% of patients had not resumed their professional activity, and 27% had returned to work but with adaptations (different position, part-time work schedule) or a complete career change.

Regarding sports, 27% of patients had resumed sports or physical activities.

4.5. MIF and SF-12

Non-parametric comparison tests showed a relationship between the FIM scores and the elapsed time after septic shock, at the limit of significance (p=0,082). We observe that the total FIM score of subjects who had a septic shock >24 months before the study is greater than that of subjects who had a septic shock ≤24 months, at the limit of significance. However, no significant relationship was found for gender.

The parametric comparison tests (Student's T test, ANOVA) did not show a significant relationship of SF-12 scores with gender, nor with the elapsed time after septic shock. Correlation of main parameters

The physical SF-12 score was negatively and significantly correlated with age (r = -0,77, p-value < 0.001). Consequently, the more the age of the patient increases, the more the physical SF-12 score decreases.

We observed a significant negative correlation between the FIM scores (total and motor) and the amputation score: the higher the amputation level, the lower the total FIM score (r = -0,59, p-value = 0.02).

The same correlations were calculated in sub-groups according to the elapsed time after septic shock in order to determine if correlations appeared 2 years or more after amputation.

We note that for subjects who had a septic shock ≤24 months: the elapsed time (in months) is negatively and significantly correlated with the mental SF-12 score (r = -0,71, p-value = 0,05).

We also observe that in these subjects, the elapsed time (in months) is negatively correlated with the total FIM score and the FIM motor score (r = -0,76, p-value = 0,03).

In subjects whose elapsed time after septic shock is >24 months, the time (in months) is negatively correlated with the physical SF-12 score, at the limit of significance (r = -0,71, p-value =

 doi:10.20944/preprints202312.1452.v1

0,09). The elapsed time is positively correlated with age of amputation, at the limit of significance (r = 0,75, p-value = 0,07).

We also note that in these subjects, the physical SF-12 score (in months) in positively correlated with the total FIM score and the FIM motor score in particular (r = 0,83, p-value = 0,02). Finally, in these patients, we observe that the total FIM score and the FIM motor score in particular are negatively correlated with the date of amputation (r = -0,90, p-value = 0,006).

4.6. Latent class analysis

Class 1: this class represents 71% of the subjects of the study. It represents the majority of male patients (55% of men), as well as the majority of patients whose elapsed time after septic shock is >24 months (55% in class 1 versus 25% of subjects in class 2). It is characterized by the highest average total FIM scores and FIM motor scores (113,42 in class 1 versus 91,04 in class 2 and 78,51 in class 1 versus 56,77 in class 2, respectively) and by a greater probability of having a low amputation score (8,35 in class 1 versus 11,22 in class 2).

Class 2: this class represents 29% of the subjects of the study. It represents the majority of female patients (75% of women), as well as the majority of patients whose elapsed time after septic shock is ≤24 months (75% in class 2 versus 25% of subjects in class 1). It is characterized by the lowest probability of having a high total FIM score and a high FIM motor score. Unlike class 1, this second class is characterized by the highest average amputation score.

5. Discussion

A growing number of patients is referred to our prosthetics institute after undergoing multiple amputations due to septic shocks: 5 patients from 1980 to 1989, 8 patients from 1990 to 1999, 15 patients from 2000 to 2009, and 35 patients from 2010 to 2018. These data are consistent with those found in the literature, which show a steady increase in the rate of septic shocks in intensive care units in the past 20 years (15). Studies also report a significant decrease in mortality in intensive care probably related to the optimization of patient care in intensive care units (15,29).

In our study, the majority of patients (71.4%) had four limb amputations, including 80% of bilateral transtibial amputations. However, thanks to the prostheses, all of the patients were able to resume ambulation even over short distances, within an average of 8.4 months [±6,25]. None of the patients were completely dependent on electric or manual wheelchairs, 40% of them did not require technical assistance for walking, and a third reported that they did not have any walking distance limit. These good functional results are probably partly due to the advances in the field of prostheses. Today, these include new equipment such as Energy storage and return (ESR) prosthetic feet offering better balance, or more comfortable prosthetic sleeves facilitating the autonomy of patients during fitting.

In the upper limbs, the levels of amputation were more diverse, and ranged from phalanx amputation to transradial amputation. The prosthetic device fitting of upper limbs usually takes place later for amputees because the main objective is their rehabilitation and independence in daily life activities without prosthetics. The means implemented are laterization when possible (e.g., injury-induced hand dominance transfer), and then the creation of technical assistive devices (e.g., pen and utensil holders). In the case of patients with distal amputation levels (amputations of the fingers/carpus), cosmetic prostheses are proposed (silicone finger or partial hand prostheses). However, their advantage is questionable since these are either refused straightaway or abandoned, as patients prefer to use their residual limb in order to preserve sensation feedback which is deemed essential. Sensation feedback is not always made possible by current prostheses and it is a major research area in addition to the improvement of prosthetic limbs control.

The effectiveness of prostheses seemed unequivocal in patients with proximal amputations (transradial amputations) who benefited from a functional prosthesis, such as a myoelectric prosthetic hand.

 doi:10.20944/preprints202312.1452.v1

A lack of specific scales for amputees is reported in the literature (30). As such, we used generic scales: the total FIM score and FIM motor score (27) for functional independence, and the SF-12 survey on quality of life.

Younger patients exhibited a better functional independence but only a long time after their septic shock (>24 months). A more distal level of amputation seemed to improve functional recovery. Patients who showed a better functional independence had a better physical quality of life, especially when their septic shock was over two years ago or more.

The results of the SF-12 survey on quality of life showed that all patients had a physical score below 50, and therefore lower than that of the general population. However, the younger the patients were, the better their physical quality of life was.

Almost half (47%) of the patients got a mental and social quality of life score above 50, thus higher than the average score for the general population. Patients with proximal amputation levels had a better mental and social score.

These results could be explained by the profile of "surviving" patients, whose difficulties in life (disease and subsequent challenges) build strong character. In addition, the selection process may be biased, since patients with a better mental and social quality of life may be more inclined to participate in a study. These results could also be explained by a better multidisciplinary care thanks to the different specialists attending to the patient which optimizes treatment during intensive care, allows for better orthopaedic surgery, and improves rehabilitative care and prosthetic management.

This monocentric study only focuses on an adult population but was performed in a prosthetics centre with strong expertise in amputee care. The statistical power is limited by the small population size due to the scarcity of quadruple amputations. Furthermore, it is only a retrospective study, since these cases are extremely rare and prospective studies would be hardly achievable.

This study is subject to other limitations. During the selection process, several patients were lost to follow-up and refused to participate in the study, which may probably affect the results regarding quality of life and independence. In addition, the questionnaires used in this study are not specific to amputee populations, some aspects which were not necessarily studied might have impacted the results. Finally, we lacked hindsight for upper limb protheses, since most patients had not received them yet at the time of the study.

The retrospective nature of the information (level of amputation, time it took to resume walking) collected through computerized medical records did however make it possible to compile complete data and limit measurement bias (failure to memorize).

6. Conclusion

Only few studies are available on adult quadruple amputees. Our preliminary study opens research perspectives and new opportunities to improve care for this type of patient which is becoming increasingly frequent in the field of physical and rehabilitation medicine.

The incidence rate of sepsis and septic shock in intensive care units is estimated to be 75 000 cases per year in France, 750 000 cases per year in the United-States, and probably more than 19 million cases in the world. In the United-States, 415 280 patients were hospitalized for a severe septic shock in 2003, and this number rose to 711 736 patients in 2007 (31). The increase in incidence of septic shocks in recent years (8.2% of admissions in intensive care in 1993 versus 15.4% in 2010) (15), the significant decrease in mortality in intensive care units (60.1 % in 1993 versus 39.5 % in 2010) (15) and the high prevalence of multiple amputations (28.3% to 70% according to the literature) (3) will lead physical medicine and rehabilitation (PMR) physicians to care more and more for patients with multiple limb amputations.

Multiple amputations may have severe functional repercussions for the patient, and the intensive care physician's self-perception of disability can lead to inappropriate decision-making such as the withholding or withdrawal of life-sustaining treatment. However, our study shows that with appropriate prostheses and in time, multiple amputees show satisfactory functional autonomy, and physical as well as mental/social quality of life scores close to that of the general population, especially when the patients are young.

 doi:10.20944/preprints202312.1452.v1

Prosthetic device fitting for patients with multiple amputations is complex and must be performed in a specialized centre as it raises challenging technical issues for a population of dependent and vulnerable patients. PMR physicians intervene from the beginning of care before surgery until the patient's discharge. Human, technological and financial means have significant impacts in terms of benefits on the functional independence of amputees and confirm the advantages of having multidisciplinary teams working with PMR doctors.

All the patients in this study were fitted with lower limbs and 100% resumed walking, including 40% without technical assistance, 33.3% without limitation of the walking perimeter. In addition, 27% had resumed a professional activity, 27% a physical or sporting activity and 47 % of patients had obtained a mental and social quality of life score higher than the average for the general population.

Our preliminary study therefore shows good results. A multicenter study, carried out at the national level, on the functional future and the quality of life of quadruple amputees would provide an holistic view. This would eventually make it possible to standardize the patient journey and improve care at the national scale.

Table 1. Study FIM results and SF12 results.

	FIM results		**SF-12**	
	Total (n =126)	**Motor (n = 91)**	**Physical (n =126)**	**Mental an social (n = 126)**
Average score ± Standard deviation	107.3 ± 14.0	72.6±13.7	36.0 ± 7.4	48.1 ± 14.1
(Min : Max)	(71 : 121)	(36 : 86)	(25.5 : 49.4)	(20.5 : 68.7)
Median	110	76	34.9	47.4
(Q1 : Q3)	(104.5 : 118)	(69.5 : 83)	(30.7 : 39.9)	(37.7 : 58.4)

Table 2. : Study population characteris.

	Class 1 (n=11, 71%)	**Class 2 (n=4, 29%)**	**p-value**
	Percentage (%)		
Woman	45.5	75.0	
Man	54.5	25.0	0,57
Time (months) ≤24	45.5	75.0	
Time (months) >24	54.5	25.0	0,57
	Average		
Age amputation (years)	45.4	47.9	0,79
SF-12 physical	36.9	33.4	0,46
SF-12 mental	47.0	51.0	0,69
FIM total score	112.4	91.0	0,02
FIM motor	78.5	56.8	0,02
Amputation score	8.4	11.2	**0,009***

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Table 3. : Correlation table of the main parameter for the all population.

Age	R							1
	p-value							-
Elapsed time after septic shock	R						1	0,08
	p-value						-	0,79
SF-12 physical	R					1	-0,15	-0,77
	p-value					-	0,59	**<0,001****
SF-12 mental	R				1	-0,03	-0,23	-0,01
	p-value				-	0,93	0,41	0,98
FIM motor	R			1	0,18	0,39	0,16	-0,18
	p-value			-	0,51	0,15	0,58	0,51
FIM total score	R		1	1	0,18	0,39	0,16	-0,18
	p-value		-	**<0,001****	0,51	0,15	0,58	0,51
Amputation score	R	1	-0,59	-0,59	0,36	-0,19	-0,23	0,25
	p-value	-	**0,02***	**0,02***	0,19	0,5	0,4	0,39
		Amputation score	**FIM total**	**FIM motor**	**SF-12 mental**	**SF-12 physical**	**Elapsed time**	**Age**

Table 4. : Correlation table of the main parameter for subjects whose elapsed time after septic shock is >24 months.

							> 24 months	
Age	R							1
	p-value							-
Elapsed time after septic shock	R						1	0,75
	p-value						-	0,07
SF-12 physical	R					1	-0,71	-0,75
	p-value					-	0,09	0,07
SF-12 mental	R				1	0,07	0,21	-0,21
	p-value				-	0,91	0,66	0,66
FIM motor	R			1	0,02	0,83	-0,65	-0,9
	p-value			-	0,97	**0,02***	0,12	**0,006***
FIM total score	R		1	1	0,02	0,83	-0,65	-0,9
	p-value		-	**<0,001****	0,97	**0,02***	0,12	**0,006***
Amputation score	R	1	-0,58	-0,58	0,6	-0,27	0,38	0,38
	p-value	-	0,17	0,17	0,15	0,55	0,4	0,4
		Amputation score	**FIM total**	**FIM motor**	**SF-12 mental**	**SF-12 physical**	**Elapsed time**	**Age**

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Table 5. : Correlation table of the main parameter for subjects whose elapsed time after septic shock is <=24 months.

		Amputation score	FIM total	FIM motor	SF-12 mental	SF-12 physical	Elapsed time	Age
								< 24 months
Age	R							1
	p-value							-
Elapsed time after septic shock	R						1	-0,33
	p-value						-	0,42
SF-12 physical	R					1	0,1	-0,65
	p-value					-	0,82	0,08
SF-12 mental	R				1	-0,19	-0,71	0,13
	p-value				-	0,67	0,05	0,75
FIM motor	R			1	0,33	0,19	-0,76	0,22
	p-value			-	0,43	0,67	**0,03***	0,61
FIM total score	R		1	1	0,33	0,19	-0,76	0,22
	p-value		-	**<0,001****	0,43	0,67	**0,03***	0,61
Amputation score	R	1	-0,33	-0,33	0,41	0,04	-0,1	-0,14
	p-value	-	0,42	0,42	0,32	0,93	0,81	0,74

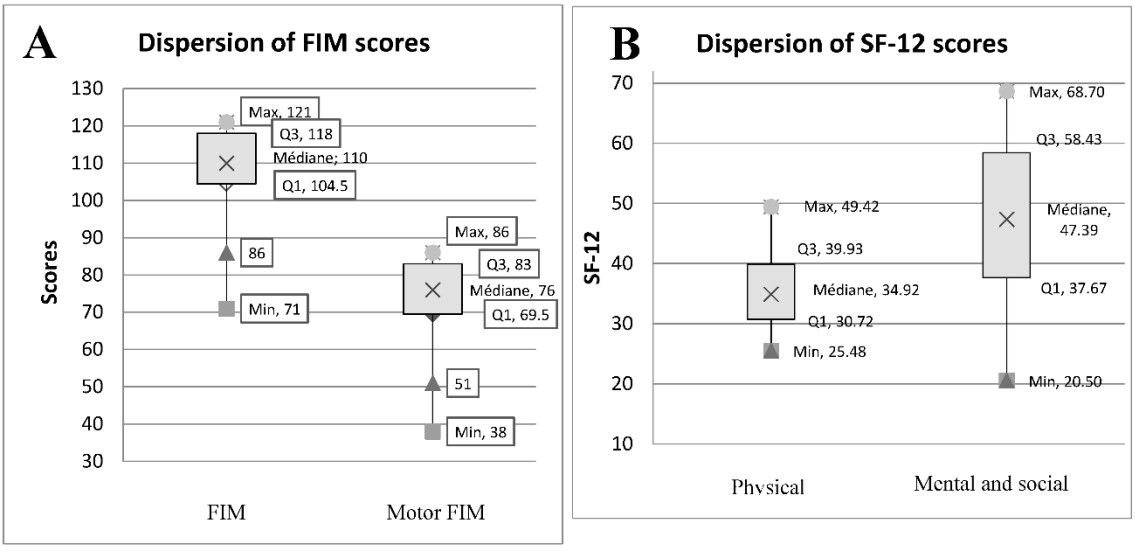

Figure 1. FIM (A) and SF-12 (A) score boxplots.

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

Institutional Review Board Statement: We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

Conflicts of Interest: We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

 doi:10.20944/preprints202312.1452.v1

Abbreviation

DIC	Disseminated Intravascular Coagulation
FIM	Functional Independence Measure
PMR	Physical Medicine and Rehabilitation
PF	Purpura Fulminans
SPG	Symmetrical Peripheral Gangrene
SF-12	12-item short-form survey to assess quality of life

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