Long-term Health-related Quality of Life and Burden of Disease After Intensive Care: Development of a Patient-reported Outcome Measure.

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Research

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Abstract

Background

ICU survivorship includes a diverse burden of disease. To understand the extent of the problems, the right issues must be identified, and the right questions need to be asked to the patients. Current follow-up instruments lack detailed questions in several areas relevant to survivors. Our aim was to identify health-related problems relevant and unique to ICU survivors, and to construct a comprehensive questionnaire able to address these issues.

Methods

Thirty-three ICU survivors were interviewed at least six months after ICU discharge. All types of everyday dysfunctions and disabilities were extracted and compiled into a questionnaire. The questionnaire was tested on ICU survivors and non-ICU treated subjects. Inclusion criteria for the ICU survivors were an ICU stay of at least 72 hours with the ICU discharge six months to three years prior to the study. The non-ICU treated subjects were obtained from the Swedish Population Register, matched for age and sex. Eligible participants received an invitation letter and were contacted by phone. If willing to participate, they were sent the questionnaire.

Results

Analysis of the interviews yielded 238 questions in 13 domains: cognition, fatigue, physical health, pain, psychological health, activities of daily life, sleep, appetite and alcohol, sexual health, sensory functions, gastrointestinal, urinary tract and work life.

In total, 395 of 518 ICU survivors and 197 of 231 non-ICU treated subjects returned a completed questionnaire, the response rate being 76.2% and 85.3% respectively. The two groups differed significantly in 16 of 25 comorbidities. ICU survivors differed in a majority of questions ($p \leq 0.05$) compared to non-ICU treated subjects, distributed over all 13 domains.

Conclusions

This study describes the first step in developing a designated questionnaire for identification of health-related quality of life issues and long-term burden of disease after intensive care.

A first version of the questionnaire was answered by 395 ICU survivors. The questionnaire could identify that they experience severe difficulties in a wide range of domains compared to non-ICU treated subjects.

Trial registration

ClinicalTrials.gov Ref# NCT 02767180

Introduction

ICU survivorship may come at a price - the price of cognitive[1] and physical dysfunction[2], psychiatric and psychological problems[3], financial and work-related shortcomings[4], and primary and hospital care consumption.[5] The ability to properly comprehend the extent of the problems relies on asking the right questions.

To describe the extent of these problems, the intensive care community uses a synthesis of tests, examinations and questionnaires depending on the context. How to measure sequelae within physical, cognitive and mental domains is guided by the concept of PICS (Post Intensive Care Syndrome) with SF-36 and EQ-5D questionnaires being the most commonly used instruments for measuring HRQoL (Health-Related Quality of Life). [6] [7] While PICS is a framework, pointing out directions for specific investigations rather than providing scales, concerns regarding the ability of SF-36 and EQ-5D to identify problems valued by ICU survivors have been raised[8]. An ICU-specific questionnaire based on patient-reported outcomes has been called for.[5] [6]

We hypothesized that a questionnaire based on narratives from ICU survivors would frame a majority of issues experienced and valued by ICU survivors. It should be practical in a scientific setting for evaluation in long-term follow-up after intensive care and be able to discriminate health related issues in ICU survivors from those experienced by non-ICU treated subjects.

Influenced by advances made in oncology[9], we applied an established methodology[10] using interviews to identify and extract issues important to survivors. In an attempt to encase the full extent of the problems, interviews were not limited to any particular areas.

Our aim of this study was to develop a questionnaire based on the factual content of such narratives on HRQoL and burden of disease issues after intensive care, and to test it in a cohort of ICU survivors and non-ICU treated subjects as a first step towards a comprehensive ICU follow-up instrument.[11] [12] [13]

Methods

INTERVIEWS AND DEVELOPMENT OF THE QUESTIONNAIRE

Intensive care survivors with a length of stay longer than 72 hours, attending the post-ICU clinic of a 16-bed mixed ICU in a university hospital at least six months after discharge, were eligible for the study. Using a purposive, maximum variation sampling approach, potential interviewees representative for different ages, admission diagnoses and time from ICU discharge were invited to participate. [14] They were selected by one of the researchers (JM) with regards to willingness and ability to share information during the visit. Sample size was based on data saturation. Between February and May in 2015, interviews were conducted either in the post-ICU clinic or in their home, based on the interviewee's own choice. Using a semi-structured technique, we explored their present situation, current symptoms or difficulties, quality-of-life, and social function. Interviews were started with open-ended questions, but as they progressed, details about findings were sought for. Once the interviewee could think of nothing

further general themes from previous interviews were discussed to potentially evoke memories and details, thus making the interviews inductive. There was no time limitation for the interviews. Additionally, issues from literature, other questionnaires and scales were discussed **(Table S1)**.

As interviews were conducted, they were sorted qualitatively:[15] Notes were taken during interviews in addition to verbatim transcription of the recorded interviews. Long quotations were shortened while preserving the core meaning of the issues and care was taken to maintain the wording used by the interviewee. Quotes from notes and transcripts with similar themes were grouped into categories ("domains") and sub-categories ("issues"). Duplicate issues were removed, and the remaining issues were formulated as questions.[1]

[1] E.g. **Quote:** "*My normal social life doesn't really work anymore, I get too tired*" → **Domain:** *Fatigue* → **Issue:** *Fatigue affecting social life* → **Question:** *"Have fatigue affected your social life, in the past month?*

Response scales were created to match each question as closely as possible using incidence, prevalence, intensity and agreement when applicable **(Table 1)**.

The time frame used in most response scales was "the last month". Care was taken not to overlap between alternatives and to include "Not applicable" if needed.

Composite questions about domain-specific quality of life and domain-specific future concerns were added at the end of each domain. Empty space and a request for missing issues or other comments were provided after each domain. Questions regarding background characteristics and comorbidities were added at the end of the questionnaire.

All questions were tested with cognitive interviews on additional ICU survivors to ensure that the questions were conceptually clear, easily understood, perceived as relevant as well as comprehensive.[16] The additional interviewees were chosen with the same criteria as the initial interviewees, and interviews were recorded as well.

APPLICATION OF THE QUESTIONNAIRE

Eligible patients were adult ICU survivors admitted between February 2013 and December 2015 to one of three mixed ICUs in Sahlgrenska University Hospital, Gothenburg, Sweden (in total 31 ICU beds), and with a minimum ICU length of stay of 72 hours. They all had been discharged from the ICU between six months and three years prior to the study. Exclusion criteria were primary neurological/neurosurgical reason for admission, limited understanding of Swedish as judged by study personnel, no Swedish personal identity number, no Swedish address or phone number, or a secret Swedish personal identity. The non-ICU treated subjects were obtained from the Swedish Population Register, matched for age and sex with respect to ICU survivors returning a completed questionnaire. For the version of the questionnaire addressing the non-ICU treated subjects we removed all questions specific to a previous ICU stay (e.g.

Have you had difficulties describing your ICU experiences?) and added one question checking for previous intensive care.

All eligible participants received an initial letter with information about the study, and within a week they received a phone call asking for participation. The questionnaire was sent together with a pre-paid return envelope, and reminder phone calls were made if the questionnaire was not returned within two weeks. The questionnaire was sent to the ICU survivors between April 2016 and October 2017, and to the non-ICU treated subjects between March 2017 and December 2017.

STATISTICAL ANALYSIS

Univariate descriptive statistics are presented as frequencies and percentages for all categorical variables. Continuous variables were screened for normality using Shapiro-Wilks ($p > 0.05$) and box-plots. For non-normally distributed continuous variables median and range or median and interquartile range (IQR) are reported. Bivariable comparisons were made between ICU survivors and non-ICU treated subjects for all ordered categorical variables and continuous variables in order to identify differences between the groups by applying the Mann-Whitney-U-test. These results are presented as means and mean rank sums and the associated p-value calculated in the Mann-Whitney-U-test. In addition, all the bivariable comparisons for ordered categorical variables were analyzed with Fisher's exact test as a robustness check. Dichotomous variables were also assessed with Fisher's exact test. All tests were two-tailed, and significance level was set to 0.05.

Questionnaires were scanned with Remark Office OMR (Remark Office OMR 10, Gravic Inc, Malvern, USA). Statistical analyses were performed using the IBM SPSS v26 package (IBM SPSS v26 Statistics, IBM, Armonk, USA).

Results

INTERVIEWS AND DEVELOPMENT OF THE QUESTIONNAIRE

All invited patients accepted to be interviewed. In total, 33 interviews including six cognitive additional interviews were performed. Minor language corrections were made based on the cognitive interviews, but no new questions were added.

The median age of the interviewees was 55.5 years (range 20-82), and 33% were females. The interviews took place at a median of 14.7 months (range 7.6-68.0) after ICU discharge. The median ICU length of stay was 4.9 days (range 1.7-76.1), and the median SAPS 3 score was 57.5 (range 24-81). Seventy per cent were treated with mechanical ventilation for a median time of five days (range 1-62). The most common primary diagnosis was infection/sepsis (18.8%), followed by trauma and cardiac arrest as second and third most common (both 12.5%) diagnosis **(Table 3)**.

The interviews generated 437 quotes including duplicates and similarities. In the qualitative sorting process, these quotes were reduced to 195 questions in 13 domains: cognition, fatigue, physical health, pain, psychological health, activities of daily life, sleep, appetite and alcohol, sexual health, sensory functions, gastrointestinal, urinary tract and work life.

For the questionnaire, 31 composite questions regarding domain-specific quality of life and domain-specific future worries were added. Also, 12 questions from other scales were added: Four questions from the KATZ-ADL index[17], all three questions from AUDIT-C[18], four questions from the Work Ability Index[19], and one question about the ability to walk for six minutes[20]. The distribution of questions is shown in **Table 2.** Twenty questions related to a previous ICU-stay per se were removed in the questionnaire for the non-ICU treated subjects.

A majority of questions was measured on an ordered category-scale: 113 questions on a 6-point scale, 91 questions on a 5-point scale, eight questions on a 4-point scale, two questions on a 3-point scale. Twenty-two questions were measured on a dichotomous scale and 2 questions were quantitative. Higher scores indicated higher levels of difficulties or problems, except in eleven reversely coded questions where higher scores indicated lower levels of problems (e.g. *Do you have the ability to look forward to things?*; *No – Rarely – Sometimes - Quite often - Very often - All the time*).

APPLICATION OF THE QUESTIONNAIRE

A total of 518 ICU survivors and 289 non-ICU treated subjects received a questionnaire. Three hundred and ninety-five ICU survivors and 195 non-ICU treated subjects returned a completed questionnaire, the return-rates being 76.2% and 85.3%, respectively **(Figure 1)**. The most commonly stated reason for declining participation among ICU survivors was family members declining (1.8%; 10 of 567) and among non-ICU treated subjects the reason was "No time" (2.2%; 6 of 276).

The most frequent ICU admission diagnosis was infection/sepsis (27.8%; n = 110) followed by trauma (13.4%; n = 53) and respiratory failure (10.9% ; n = 43) Median SAPS 3 score was 59 (range 16-100), and median ICU length of stay was 5.6 days (range 3.0-78.6). Most ICU survivors were mechanically ventilated (78.5%), with a median time of 4.0 days (range 0-74). Only minor differences could be seen in ICU admission diagnosis between the interviewee group and the ICU survivor group.

There were no differences in age and gender between the ICU survivors and the non-ICU treated subjects **(Table 4a)**. At the time of completing the questionnaire, the ICU survivors were sicker, differing in 16 of 25 comorbidities ($p \leq 0.05$) **(Table 4b)**.

A complete list of questions their response rates is shown in **Table S2a/b.** The answers differed significantly between ICU survivors and non-ICU treated subjects in a majority of questions across all domains **(Table S2a and Table 5)**. All continuous variables were found to deviate from normality in both groups.

No additional valuable information was added to the space after each domain.

Discussion

Our study describes the first step towards an intensive care long-term follow-up questionnaire with the capacity to detect the burden of ICU survivorship and the effect on quality of life. By creating a questionnaire from interviews with ICU survivors and testing it in a cohort study, we were able to show the questionnaire to be both feasible, containing most issues important to survivors, and able to discriminate ICU survivors from non-ICU treated subjects.

At a stakeholders' conference in 2010, the concept of PICS was created to enclose impairments in mental health, cognition and physical functions.[21] At a follow-up conference in 2012, the PICS group pointed out the need for outcome assessment tools created with qualitative methods. Several groups have addressed this issue, either by developing new instruments or by examining the content validity of existing ones. Jeong and Kang reported the development and validation of a questionnaire specifically for the three domains of PICS, using a methodology similar to ours.[22 23] In 2018, Nedergaard et al. interviewed 18 ICU survivors and extracted the most important issues.[24] Although symptoms from the PICS domains were well represented, additional symptoms were also considered important, for example incontinence, short temper and the feeling of being isolated. Furthermore, large differences between patients and clinicians when ranking the importance of symptoms have been found in areas as diverse as bariatric surgery[25], diabetes[26] and aphasia.[27] These findings would argue toward instruments developed with the input from survivors.

Regarding measuring HRQoL, SF-36 and EQ-5D are currently the most commonly used tools after intensive care. Lim et al. extracted post-ICU issues from 30 ICU survivors and let the same patients compare these issues with SF-36 and EQ-5D.6 Of the domains identified as relevant by the ICU survivors, only one was considered adequately covered by SF-36 or EQ-5D. The remaining domains were either inadequately covered or completely missing, suggesting that the use of either of these instruments as a measurement of post-ICU HRQoL will miss important effects. Indeed, Jensen et al. were unable to show improvement in HRQoL measured by SF-36 after their ICU recovery program and recommend new instruments to be developed and validated to assess the particular HRQoL problems of post-ICU patients.[5]

Our questionnaire focuses on different measures of ICU survivorship: First of all, it covers the areas of PICS; physical, cognitive and mental health. Secondly, it describes quality-of-life related to the survivor's health status. Lastly, areas not covered by PICS or SF-36/EQ-5D such as dysphagia[28], joint contractions[29], sleep disturbances[30] and personal finances[31] are included, all previously described problems after intensive care.

Strengths

The response rate of 76.2% from the ICU survivors and 85.3% from the non-ICU treated subjects indicates not only the feasibility of using the questionnaire in a trial context, but that questions were considered relevant. Participants did not provide any missed issues in the comment areas in the questionnaire, only encouraging comments, arguing towards a high level of content validity in our questionnaire rather than "questionnaire fatigue".

The development of the questionnaire follows international recommendations for development of patient-reported outcome measures.[32] Choosing interviewees purposively instead of randomizing or in consecutive order has been the most effective in simulations.14 Data saturation is the most commonly used delimiter for sample size but not randomizing the order of the interviews poses a hypothetical risk of affecting the saturation point.[33] Therefore, we decided à priori to set the sample size to whenever three consecutive interviews did not provide any new information.

Limitations

A limitation of the current questionnaire is the number of questions. Even if a high response rate indicates the relevance of the questions asked as well as the feasibility of using the questionnaire in a trial context, our questionnaire will be reduced for research and clinical use. Differences in comorbidities between ICU survivors and non-ICU treated subjects, where 16 of 25 differed significantly, align with previous findings that chronic comorbidities are common in ICU patients. [34] The questionnaire has not been developed from, nor tested on, patients with a shorter time from ICU discharge than six months, hence our questionnaire may miss issues that resolve completely within this time frame. Nor was the questionnaire developed for patients with an ICU length of stay shorter than 72 hours or with neurological/neurosurgical primary diagnoses, and results cannot be generalized to these groups. Regarding internal validity, there was a difference in age between the interviewees and the cohort groups. However, ranges of age, SAPS score etc. did not differ markedly. Lastly, we cannot exclude a selection bias with regards to patients who chose not to participate or who we were unable to reach.

Conclusion

This study describes the first step in developing a specific questionnaire for long-term HRQoL and burden of disease after intensive care. The first version based on problems identified by interviews with ICU survivors clearly could identify burden of disease affecting multiple domains in a cohort of patients. After a future reduction of the number of questions, this instrument may be a useful tool in follow-up after intensive care.

Abbreviations

ADL: Activities of Daily Living

EQ-5D: EuroQoL's five dimensions instrument

ICU: Intensive Care Unit

HRQOL: Health-Related Quality of Life

PICS: Post Intensive Care Syndrome

PTSD: Post-Traumatic Stress Disorder

SAPS 3: Simplified Acute Physiology Score

SF-36: Short Form (36) Health Survey

Declarations

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Authors' contributions

J.M. and A-C.W. developed the questionnaire. J.M., A-C.W. and S.L. designed the study. J.M. collected the data. All authors contributed to the interpretation of the data. E.J. performed the data analysis. J.M. and A-C.W. wrote the manuscript. A-C.W., S.L., C.R., and E.J. critically edited and revised the manuscript. All authors read and approved the final manuscript.

Availability of data and materials

The datasets generated during and/or analysed during the current study are not publicly available due them containing information that could compromise research participants privacy/consent, but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The two parts of the study were approved by the Regional Research Ethics Committee of Gothenburg, Sweden, on February 26, 2015 (Ref 017-15) and February 23, 2016 (Ref 011-16), respectively. The second part is registered in Clinical Trials Gov (Ref. NCT 02767180).

Interviewed participants were given oral and written information concerning their participation in the study. Consent in the applicatory part was assumed by the return of a completed questionnaire. Data was handled and stored according to the European General Data Protection Regulation (GDPR).

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Tables

Table 1 Examples of wordings and response scales of questions asked in the questionnaire.

Measure	Question	Response scale
Incidence	Have you had leakage of stools because of not being able to reach the toilet in time?	No – Occasionally – Once a week – Several times a week – Once a day – Several times a day
Prevalence	Have you needed help moving between chair and bed	No – Occasionally - Half of the times - Most of the times - Every time
Intensity	Have you found normal touch bothersome?	Not at all – A little – Moderately – Quite a bit – Very much
Agreement	Do you have difficulties extending your wrist?	No – Yes

Table 2 Domains and number of questions in the questionnaire sent to ICU survivors.

Domain	Number of questions
Cognitive function	31
Fatigue	14
Physical health	31
Pain	19
Psychological aspects	29
Activities of daily living (ADL)	16
Sleep	11
Appetite and alcohol	11
Sexual health	14
Sensory functions	26
Gastrointestinal	7
Urinary tract	8
Work life	21
Total number of questions	**238**

Table 3 Clinical characteristics of ICU survivors and interviewees.

Primary diagnosis, n (%)	ICU survivors (n=395)	Interviewees (n=33)
Infection/sepsis	110 (27.8)	6 (18.8)
Trauma	53 (13.4)	4 (12.5)
Respiratory failure	43 (10.9)	3 (9.4)
Major bleeding[1]	38 (9.6)	0 (0.0)
Cardiac arrest	24 (6.1)	4 (12.5)
GI diseases[2]	17 (4.3)	3 (9.4)
Liver failure	16 (4.1)	1 (3.1)
Transplantation	16 (4.1)	3 (9.4)
Postoperative	16 (4.1)	1 (3.1)
Renal failure	12 (3.0)	3 (9.4)
Pulmonary diseases[3]	10 (2.5)	0 (0.0)
Cardiac failure and/or myocardial infarction	10 (2.5)	2 (6.3)
Vascular disorders[4]	10 (2.5)	0 (0.0)
Metabolic disorders	8 (2.0)	0 (0.0)
Other	7 (1.8)	2 (6.3)
Oncological or hematological disorders	5 (1.3)	0 (0.0)
SAPS3 score		
Median (range)	59 (16-100)	57.5 (24-81)
ICU, length of stay		
Days, median (range)	5.5 (3.0-78.6)	4.9 (1.7-76.1)
Mechanical ventilation		
Patients, *n* (%)	310 (78.5)	23 (69.7)
Days, median (range)	5.0 (1.0-74.0)	5 (1.0-62.0)
Continuous Renal Replacement Therapy		
Patients, *n* (%)	88 (22.3)	11 (33.0)
Days, median (range)	6.0 (1.0-42.0)	8.0 (3.0-53.0)

[1] including aortic rupture and GI bleeding; [2] including pancreatitis and peritonitis; [3] including COPD and pneumonitis; [4] including emboli and thrombi.

Table 4a Demographics at the time of answering the questionnaire.

	ICU survivors (n=395)	Non-ICU treated subjects (n=195)	p-value	Total (N)
Age, years; median (IQR)	65.0 (18)	65.0 (15)	0.56	589
Body mass index; median (IQR)	26.0 (7)	25.4 (5)	0.17	555
Smoker; n (%*)	15 (13)	15 (11)	0.01	109
Male; n (%*)	239 (61)	117 (60)		
Education; n (%*)				
Elementary school	138 (31)	53 (22)	0.05	592
Primary and junior secondary school	27 (6)	17 (7)	0.51	592
Vocational education	43 (10)	27 (11)	0.35	592
Upper secondary school	97 (22)	51 (21)	0.76	592
College or University	125 (28)	73 (31)	0.20	592
Other	19 (4)	18 (8)	0.05	592
Employment status; n (%*)				
Contract employment	50 (15)	47 (26)	0.00	592
Self-employment	13 (4)	11 (6)	0.19	592
Sickness benefit	42 (12)	4 (2)	0.00	592
Student	4 (1)	1 (1)	1.00	592
Unemployed (out of work)	2 (1)	1 (1)	1.00	592
Sick leave	22 (7)	1 (1)	0.00	592
Parental leave	2 (1)	3 (2)	0.34	592
Retired	163 (48)	87 (48)	0.54	592
Occupational pension	40 (12)	28 (15)	0.17	592
Current form of living; n (%*)			0.00	575
Hospital	2 (1)	0 (0)		
Rehab	3 (1)	0 (0)		
Nursing home	3 (1)	0 (0)		

Residential home	13 (3)	1 (1)		
Apartment	187 (49)	53 (28)		
Detached house	176 (46)	137 (72)		
Civic status, n (%)*				
Married/partner	233 (63)	159 (84)	0.00	545
* percent of responding participants.				

Table 4b History of comorbidities at the time of answering the questionnaire.

	ICU survivors (n=395)	Non-ICU treated subjects (n=195)	p-value
Cardiovascular, n (%*)			
Hypertension	183 (46)	60 (31)	0.00
Angina pectoris	28 (7)	5 (3)	0.03
Myocardial infarction	52 (13)	4 (2)	0.00
Heart failure	56 (14)	11 (6)	0.00
Asthma	34 (9)	19 (10)	0.00
Respiratory, n (%*)			
Lung disease, e.g., COPD, bronchitis	50 (13)	5 (3)	0.00
Pulmonary embolus	21 (5)	1 (1)	0.00
Sleep apnea	35 (9)	15 (8)	0.64
Home ventilator	7 (2)	0 (0)	0.10
Neurological, n (%*)			
Stroke	34 (9)	11 (6)	0.25
Dementia/Alzheimer's disease	2 (1)	3 (2)	0.36
Multiple sclerosis	2 (1)	2 (1)	0.60
Parkinson's disease	3 (1)	1 (1)	1,00
Psychiatric, n (%*)			
Psychological diseases, e.g. depression, anxiety	65 (16)	17 (9)	0.01
Metabolic, n (%*)			
Non-insulin dependent diabetes	53 (15)	14 (8)	0.03
Insulin dependent diabetes	43 (11)	4 (2)	0.00
Kidney disease	33 (8)	3 (2)	0.00
Dialysis	6 (2)	1 (1)	1,00
Other, n (%*)			
Tumour disease	44 (11)	14 (7)	0.14
Bowel disease	42 (11)	10 (5)	0.03
Rheumatic disease	27 (7)	9 (5)	0.28

Physical walking aids, n (%*)			
Walking stick/crutches	0 (0)	0 (0)	0.00
Walking frame/rollator	69 (17)	0 (0)	0.00
Wheelchair/electric wheelchair	35 (9)	0 (0)	0.00
Bedridden	5 (1)	0 (0)	0.18
Amputated limb(s)	13 (3)	0 (0)	0.01
* percent of responding participants.			

Due to technical limitations, table 5 is only available as a download in the Supplemental Files section.

Figures

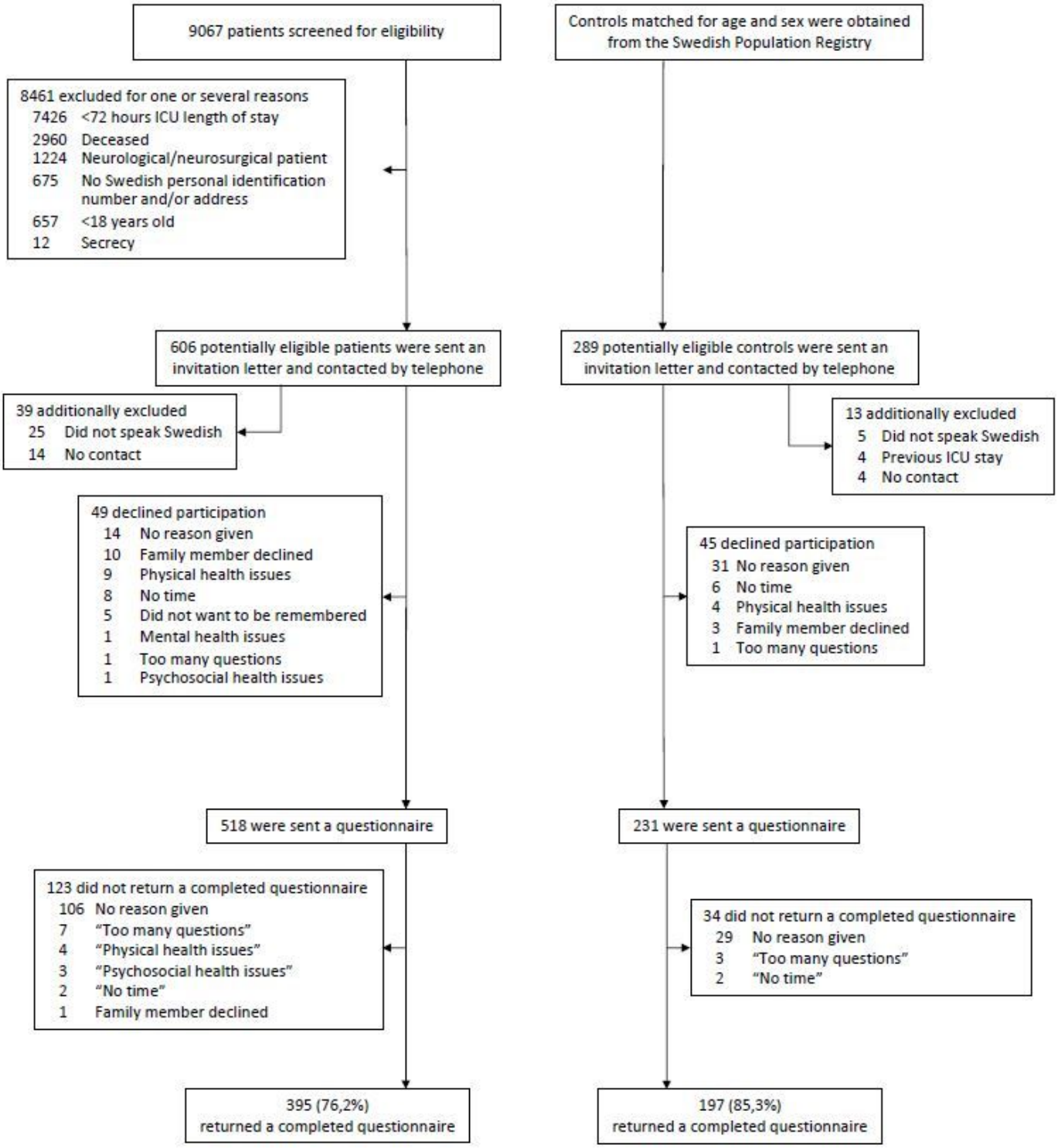

Figure 1

CONSORT diagram of screening, recruitment, follow-up and reasons for non-participation. Abbrevations: ICU - Intensive Care Unit.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- TableS1.docx
- TableS2aDescriptivestatistics.xlsx
- TableS2bDescriptivestatisticsICUspecific.xlsx
- Table5Meanranksum.xlsx