

Health Related Quality of Life and Mental Health in ICU Survivors: Post-Intensive Care Syndrome Follow-Up and Correlations between the 36-Item Short Form Health Survey (SF-36) and the General Health Questionnaire (GHQ-28)

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How to cite this paper: Tugnoli, S., Spadaro, S., Corte, F.D., Valpiani, G., Volta, C.A. and Caracciolo, S. (2022) Health Related Quality of Life and Mental Health in ICU Survivors: Post-Intensive Care Syndrome Follow-Up and Correlations between the 36-Item Short Form Health Survey (SF-36) and the General Health Questionnaire (GHQ-28). *Health*, 14, 477-506.
<https://doi.org/10.4236/health.2022.145037>

Received: January 31, 2022

Accepted: May 14, 2022

Published: May 17, 2022

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Abstract

We investigated the relationship between health-related quality of life (HRQOL) and psychological distress in intensive care unit (ICU) survivors 12 months after ICU discharge. The purpose of this study, conducted and completed before the onset of the COVID-19 pandemic, was to find correlations among psychiatric symptoms detected by a screening tool as the General Health Questionnaire-28 (GHQ-28) and the different domains of HRQOL measured with the SF-36 health survey (SF-36), in order to identify ICU survivors with Post-Intensive Care Syndrome (PICS) who need a specific psychiatric intervention to improve their HRQOL. Among 298 ICU survivors who stayed in the ICU for at least 72 hours, 48 patients were enrolled one year after discharge undergoing a clinical interview to assess their functional impairment (Barthel index), mental health (GHQ-28), and health-related quality of life (SF-36). 19% of those subjects had a GHQ-28 ≥ 5 and were identified as “psychiatric cases”, and they were older and experienced a greater impairment in HRQOL. Anxiety, insomnia, and depressive symptoms seemed to be particularly involved in the impairment of HRQOL. A negative correlation between GHQ-28 total scores and subscales and SF-36 subscales was found.

Our findings highlighted that psychological distress in ICU survivors may negatively impact physical health recovery and quality of life; conversely, physical impairment and functional disability may trigger the onset of psychiatric symptoms after discharge. The present study is firstly to investigate the correlations between HRQOL and psychological distress in ICU survivors through the GHQ-28, and then affirms the need to carry out follow-up checks for psychiatric symptoms in ICU survivors.

Keywords

ICU Survivors, Psychological Distress, Health-Related Quality of Life, SF-36 Health Survey, Scaled General Health Questionnaire (GHQ-28)

1. Introduction

Health-related quality of life (HRQOL) following discharge from the intensive care unit (ICU) is of increasing concern to scholars in the field. Over the past 20 years, much research has been conducted with the aim of assessing the impact of the ICU stay on critically ill patients, focusing on physical complications, psychological distress, negative psychological and neuropsychiatric sequelae, and on HRQOL of ICU survivors [1] [2] [3] [4]. These outcomes can lead in 30% - 50% of patients to a global impairment known as “Post-Intensive Care Syndrome” (PICS), a “new or worsening impairments in physical, cognitive, or mental health status arising after critical illness and persisting beyond acute care hospitalization” [5] [6] [7] [8], with a negative impact on long-term survivors’ quality of life [9]-[14]. In the multicenter cohort study of Marra *et al.* [15], post-intensive care syndrome problems assessed in three different domains (cognitive impairment, functional disability and depression) were present in 56% of patients 12 months after hospital discharge.

Most studies report that depression, anxiety, post-traumatic stress disorder, and cognitive impairment are common among ICU survivors [6] [10] [16]-[24], and that these psychiatric disorders are manifested both in the short term [25] [26] and in the long term [10] [27]. The prevalence of rates of depression in ICU survivors is higher than in the general population [28]-[34], with symptoms present in about 30% of post-ICU patients [35]. The duration of depressive symptoms following a critical illness is unclear, but some studies have found a reduction of these symptoms during the first year after ICU discharge [36] [37] [38] [39]. Recently, a large population-based cohort study showed that survivors of critical illness have an increased risk of suicide and self-harm if compared with non-ICU hospital survivors. This risk was associated with the increased risk of psychiatric morbidity and invasive mechanical ventilation or renal replacement therapy in the ICU [40].

Also, anxiety is a common psychopathological outcome after intensive care [10] [33] [36], with rates of symptoms ranging from 32% to 40% within the first

year after discharge [41]. Post-traumatic stress disorder, in particular, is a very common psychiatric disorder following admission to ICU [29] [32] [36] [42]-[47], with prevalence rates varying from 17% to 44% in the year after discharge [48]. The meta-analysis of Righy *et al.* [49] found that 1 in every 5 adult ICU survivors develops PTSD symptoms in the year following discharge, with an overall pooled prevalence of 19.83% and a point prevalence of 18.96% 12 months after discharge.

Jackson *et al.* [50] found that depression was four times more frequent than PTSD after critical illness. Furthermore, ICU survivors often show overlapping symptoms [15] and a high rate of depression–post-traumatic stress disorder comorbidity is observed, more than in other kinds of patients and in the general population [29] [32] [51] [52], especially in younger and in female subjects [32] [53] [54].

Long-term cognitive impairment is another frequent adverse clinical outcome of critical illness and ICU stays [55], with more frequent impairment in executive functioning, memory, and attention [56], especially in elderly patients [57] [58]. Impairments in executive functioning may have substantial life-changing effects on the patients' lives such as difficulties with planning, problem-solving, inhibition, and control of behavior that may lead to the inability to return to work or to function autonomously [59] [60].

All of the aforementioned neuropsychiatric complications can affect HRQOL in ICU survivors. Several studies show that HRQOL is commonly impaired after ICU discharge and that it is lower than in the general population [1] [2] [4] [61] [62] [63], especially in physical domains [10] [64] [65]. This impairment may persist from six months to six years post-hospital discharge [66], lasting up to 8 - 12 years after certain clinical situations (acute respiratory distress syndrome or severe sepsis) [59] [67] [68]. Often this complication becomes apparent only after ICU discharge and may improve partially over the first year post-ICU [10] [57] [61] [4]. However, HRQOL tends to improve, to some degree, in the long term to levels comparable with those of the normal population [64] [69], but such improvement is not uniform across the different domains.

There are many reasons for the higher prevalence rates of neuropsychiatric sequelae, particularly depression, in ICU survivors compared to the general population. Emotional distress reactions in the ICU should be considered, along with several patient-related psychological risk factors, as well as clinical and management factors [25] [31] [53] [70] [71], in order to provide the best care for these particular patients, during their ICU stay and after discharge.

Critical illness and intensive care can play a role in triggering negative emotional reactions in particularly vulnerable patients [29] [72] [73]. Personality traits such as pessimism [28] [54], traumatic events during childhood, recent exposure to stressful life events, a lifetime history of psychiatric disorders [29] [16] or the evidence of pre-ICU psychiatric symptoms [17] [31] [43] [61] [74] [75], are indicators of individual vulnerability to adverse psychological outcomes

after the ICU stay. In addition, elderly and frail populations may be more prone to develop post-ICU cognitive impairment due to the worsening of a pre-existing Mild Cognitive Impairment (MCI) [58].

Gender also appears to be a patient-specific factor and a predictor of psychological morbidity after critical illness [8] [10] [16] [36] [40] [54] [76] [77]. Asimakopoulou & Madianos [32] consider being female a risk factor for the onset of depression after ICU stay, finding higher prevalence rates of major depression in females compared to the overall sample in the ICU group (45.9% vs 32.3%) and detecting that “women admitted to the ICU were almost 12 times more likely to suffer from major depression and PTSD than men” [32]. However, this issue remains uncertain and contradictory. Schandl *et al.* [17] state that the female gender should not be considered an important predictor of psychological morbidity in ICU survivors, considering the fact that compared with the male gender, previous psychological problems are more common in women [78]. Furthermore, in many studies [1] patient gender does not appear to be an important predictor of quality of life in adult survivors of critical illness.

Several clinical factors related to ICU stay may be associated with negative emotional outcomes and increased severity of depression in the year following ICU discharge [3] [10] [25] [30]. They include recurrence of in-hospital acute stress symptoms, fears and trauma experienced in the ICU, frightening or delusional memories [10] [16] [17] [43] [44], the level of consciousness [32], the presence of agitated delirium [17], acute respiratory distress syndrome (ARDS) [43], cerebral hypoxia, inflammation, or hypoglycemia [10] [31] [70] [74] and severe sepsis [79]. Moreover, along with post-ICU impairment in physical function, depressive signs or symptoms in ICU and early post-ICU depressive symptoms have proven to be strong predictors for later development of depression [17] [31] [36] [80].

Finally, ICU management factors should also be taken into account, because of their possible negative impact on psychological outcome and long term quality of life [16] [25] [70] [81] [82]: the admission and the length of ICU stay, the different ways of managing the critical illness (e.g., mechanical ventilation and its duration, or treatment with benzodiazepines and duration of sedation) as well as environmental and situational factors, such as noise, light-dark cycle and disrupted sleep deprivation, limited communication skills and reduced autonomy [10] [53] [79] [83] [84].

A screening questionnaire for psychological well-being in ICU survivors is pivotal in detecting the presence of psychiatric symptoms after discharge. Hatch *et al.* [85], in a wide multi-centre prospective cohort study carried out through a postal survey at 3 and 12 months after discharge, showed “a burden of psychopathological disease in around a quarter of those who have survived a period of ICU treatment”, confirming that “there is a significant unmet psychopathological need in survivors of critical illness” and stressing the need for screening and early treatment of psychological distress in order to improve HRQOL. Aitken

and Marshall [86] stated that outcomes assessment should be a routine component of clinical practice in order to define the most appropriate interventions to promote recovery in ICU survivors. Unfortunately, there is a lack of agreement as to the precise instruments that should be used, or the time points when assessment should occur. The optimal timing of interventions and appropriate therapy with which to treat any psychiatric disease in those recovering from critical illness remains unclear [21] [86]. Peris *et al.* [87] found that early intra-ICU clinical psychologist intervention may help critically ill trauma patients to recover from this stressful experience, while Cuthbertson *et al.* [88] found no effect of a nurse-led follow-up program in improving patients' physical and psychological HRQOL in the year after ICU discharge. Considering a range of different post-ICU interventions other studies demonstrated no treatment effect as well [89] [90] [91]. Such findings have promoted awareness among clinicians regarding unresolved questions concerning the process of psychological and physical healing from critical illness and its relationship with HRQOL, an important outcome following the survival of a critical illness. A recent meta-analysis by Rosa *et al.* [92] highlights how Post-ICU follow-up is associated with improvements in depression and PTSD symptoms and mental health-related quality of life. The last Consensus Conference on post-intensive care syndrome prediction and assessment, convened in 2019 by the Society of Critical Care Medicine, provided recommendations to screening for long-term impairments of critical illness in adult survivors, following three fundamental questions related to post-hospital discharge assessments: "who should be screened for these impairments? What screening tools should be used? When should these assessments be performed?" [93].

The aim of the present study was to detect the presence of psychological distress symptoms in patients considered mentally healthy before ICU admission, as retrieved by anamnestic records, after a one year follow up period consequent to ICU discharge, finding specific correlations among some psychiatric symptoms and the different domains of HRQOL in ICU survivors. For this purpose, we used two different tools: the 28-item General Health Questionnaire (GHQ-28) [94], a well-known screening questionnaire for psychological well-being, and the 36-item Short Form Health Survey (SF-36), quality of life questionnaire widely validated in the general population [95] and formally tested and found to be adequate in the ICU setting [96]. In this way, we evaluated the utility of a quick and easy administrable psychiatric screening to identify patients with Post-Intensive Care Syndrome (PICS) who need an intervention for their psychological distress, providing, at the same time, indirect information about HRQOL of these patients because of the overlap areas of GHQ sub-scales with some dimensions of SF-36.

To the best of our knowledge, the relationship between HRQOL measured using the SF-36 survey and the presence of psychiatric symptoms examined through the GHQ-28 screening questionnaire has never been evaluated in ICU survivors. We considered a one-year follow-up period [53] [97] [98] [99] as an

adequate amount of time to limit the number of patients lost to follow-up given the elderly study population. Furthermore, one year could be sufficient to minimize the bias imposed by the incomplete recovery of physical functioning on the psychological wellbeing of our study patients.

2. Patients and Methods

2.1. Participants

A convenience sample of consecutive 423 adult ICU patients discharged in a study period of 18 months was considered for enrolment in this study, conducted and completed before the onset of the COVID-19 pandemic. Patients were included if they were more than 18 years old and had stayed in the ICU for at least 72 hours. Patients were excluded if they had a history of mental illness (*i.e.* anamnestic evidence of psychiatric disorder, use of psychotropic drugs, previous admission to a psychiatric ward) or cognitive impairment (*i.e.* MMSE < 26), a diagnosis of neurodegenerative disorders, or a history of primary neurologic injuries, and if they did not have a permanent residential address. One year after ICU discharge, the vital status of the patients was assessed and ICU survivors were contacted by phone to ask them to participate in the study. Those who agreed were given an appointment at the hospital in which to complete the interview in order to evaluate cognitive functioning, functional impairment, mental health, and HRQOL.

2.2. Procedure

We set up a cross-sectional study conducted in the mixed medical-surgical six-bed ICU of the S. Anna University Hospital in Ferrara (Italy), through a collaboration between the Anesthesiology and Intensive Care Unit and the Neurological, Psychiatric, and Psychological Sciences Section of the Department of Neuroscience and Rehabilitation, Faculty of Medicine, Pharmacy and Prevention, University of Ferrara (Italy). The demographic and clinical data of the study patients were retrieved from the ICU records. For each participant, the following information was collected: gender, age, preexisting comorbidities, type of admission, presence of infection at ICU admission, duration of mechanical ventilation and of sedation, and the use of psychotropic medication during the ICU stay. In addition, the following computed data were also retrieved: a simplified acute physiology score (SAPS II) [100] and a sequential organ failure assessment score (also known as a sepsis-related organ failure assessment score; SOFA) [101], referred to in the first 24 hours in ICU, and the length of stay (LOS), calculated as the number of days in ICU and in hospital after ICU discharge.

2.3. Measures

2.3.1. Mini-Mental State Examination

The Mini-Mental State Examination (MMSE) is a psychometric tool widely used

in clinical and research settings for an initial assessment of cognitive functions [102]. It is a 30-point questionnaire with verbal and performance items that assess several cognitive functions: orientation to time and to space, registration, attention and calculation, recall, language, repetition, naming, reading, writing, and constructional praxis. It is easy and rapid in its administration and is reliable in measuring the degree of cognitive impairment and monitoring the progression of cognitive decline. The MMSE was used in our study to evaluate the global cognitive function of participants, in order to detect possible cognitive impairment. We chose a cutoff point of a score of less than 26 (out of 30) as the criterion for detecting the presence of cognitive impairment, a value that achieves a sensitivity of 0.80 and a specificity of 0.96 in terms of the inherent validity of the diagnostic test [103].

2.3.2. Barthel Index

The Barthel index provides an indicative score of the ability of the subject in performing basic activities of daily living, encompassing feeding/eating, bathing, grooming/managing personal hygiene, dressing, toilet use, control of bowels and bladder, moving from a bed to a chair and vice versa, and mobility/walking on level ground and up and down stairs [104]. In the present study response options were scored 10 (*can perform the activity independently*), 5 (*requires some help/assistive device*), or 0 (*is unable to perform the activity on his/her own*). The total scores ranged from 0 to 100, with lower scores indicating a higher level of impairment.

2.3.3. GHQ-28

The General Health Questionnaire (GHQ) is a self-administered psychometric tool widely used around the world in screening investigations to detect the presence of psychiatric symptoms in the general population and in non-psychiatric clinical contexts [105] [106] [107] [108] [109]. It focuses on breaks in normal psychic functioning and is designed to identify an inability to carry out one's normal "healthy" functions and the appearance of new distressing phenomena. Consequently, it can identify recent changes in the normal mental functioning of a subject; however, it is not intended to distinguish among different psychiatric disorders or for diagnostic purposes.

In the present study, a 28-item scaled GHQ (GHQ-28) was used to investigate the mental health status of the subjects [94]. Somatic symptoms (SS), anxiety and insomnia (AI), social dysfunction (SDys), and severe depression (SDep) are the four seven-item subscales of the questionnaire, useful to highlight the profiles of the prevalent psychological distresses. The participants were asked to compare their current psychological condition to their habitual condition by choosing from four different answers, as follows: "better than usual", "same as usual", "worse than usual", "much worse than usual" (for positive items), or "not at all", "no more than usual", "rather more than usual", "much more than usual" (for negative items). We used the so-called "GHQ score," an alternative binary

scoring method that evaluates answers according to dichotomous coding: “0” indicating the absence of the symptom and “1” the presence of the symptom (*i.e.*, the two least symptomatic answers scoring “0” and the two most symptomatic answers scoring “1”) [109]. Total scores ranged from 0 to 28, with higher scores indicating worse psychological health. Following the initial findings of Goldberg [108] [110], the cutoff value used to identify the possible “psychiatric cases” with GHQ-28 was 4/5. This threshold allows a good balance between specificity (84.2%) and sensitivity (88%) [94], and enabled us to split our sample into two subgroups: one featuring subjects with probable psychological distress (GHQ-28 score ≥ 5) and the other comprising subjects without evidence of clinically significant psychiatric symptoms (GHQ-28 score < 5).

2.3.4. SF-36

The SF-36 (version 1) is a multidimensional self-rated health status questionnaire that refers to the four weeks prior to administration [95] [111], widely used in research and clinical practice to measure non-disease specific general health status and its outcomes. It consists of 36 questions measuring eight multi-item domains of health: 1) physical functioning (PF), or limitations in one’s ability to perform the physical activities of everyday life; 2) physical role functioning (RP), the degree to which physical health problems limit the activities that define the role of a person; 3) bodily pain (BP), the severity and the impact of physical pain on ordinary activities; 4) general health (GH), perceptions and evaluations of one’s own health; 5) vitality (VT), the degree of subjectively perceived energy; 6) social role functioning (SF), the degree to which one’s physical or emotional state of health limit normal social activities; 7) role-emotional (RE), the degree to which one’s emotional state limits the performances in daily activities; and 8) mental health (MH), the state of mental health in general.

The scores obtained with the eight scales are then aggregated to make two synthetic indices, which reassume the two major domains of the SF-36: the physical component summary (PCS), which independently evaluates physical functioning, and the mental component summary (MCS), reflecting social functioning and mental health: PCS encompasses PF, RP, and BP, whereas MCS includes SF, RE, and MH [112]. Higher scores represent better functioning. Low scores in PCS indicate limitations in self-care and in physical, social, and role activities, severe bodily pain, or frequent tiredness, while low scores in MCS indicated psychological distress, and substantial social and role disability due to emotional problems [113]. Scores for PCS and MCS have been calculated by transforming results to “norm-based data,” standardized on 50 as the population mean (U.S. population), with *SD* 10 representing one standard deviation [64] [114]. In our study, the SF-36 (version 1) survey was administered using the previously validated Italian version [115] [116].

2.4. Statistical Analyses

Normal distribution was tested using the Kolmogorov–Smirnov test. In cases of

non-normal distribution, data medians and interquartile ranges [IQR, 25th-75th percentile] were reported. For continuous and normally distributed data, the means and standard deviations ($\pm SD$) were calculated. Categorical variables were reported as absolute and relative frequencies (%). Unpaired student's *t*-tests or Mann-Whitney U tests were used to compare continuous variables, as appropriate, whereas differences in categorized variables were assessed using the chi-squared test or Fisher's exact test, as appropriate. We investigated the internal consistency of the GHQ-28 questionnaire using Cronbach's α (coefficient alpha). Non-parametric correlation analyses were calculated using the Spearman coefficient (ρ). The association between SF-36 items and the physical (PCS) and mental (MCS) component summary and the presence of psychological distress (GHQ-28 score ≥ 5) was modeled using binary logistic regression analysis and is reported as estimated odds ratio and relative 95% confidence interval (CI). A multivariate logistic regression model was used to estimate which of the items was independently associated with a GHQ-28 score ≥ 5 . The best predictors were identified by blockwise selection. Due to redundancies MCS and PCS were excluded from the final multivariate model. Statistical analyses were performed using SPSS 20.0 statistical software (SPSS Inc., Chicago, IL, USA). For all of the statistical analyses, two-tailed tests were performed and *p*-values equal to or less than 0.05 was considered statistically significant.

3. Results

During the study period, 423 patients were admitted to the ICU (see **Figure 1**). 202 of them—those who were younger than 18 years of age, those who had stayed in the ICU for fewer than 72 hours, those who had a preexisting cognitive disorder or neurodegenerative disorder and/or primary neurologic injury, and the five patients who were homeless at the time of ICU admission—were excluded. Of the remaining 221 patients, 73 died during the year after ICU discharge. Of the 148 ICU survivors one year after discharge, 41 declined to participate in the study, 19 patients were not contactable (despite multiple attempts to do so), and 35 patients had been hospitalized. One year following their discharge from the ICU, we directly interviewed 53 patients, and excluded five of them because of their attaining an MMSE score of less than 26. Ultimately, a convenience sample of 48 patients was included in the study.

3.1. Demographic and Clinical Variables

The clinical characteristics of the enrolled patients are reported in **Table 1**. The mean age of our cohort of patients was 67 ± 12 years. We enrolled 34 males and 14 females.

Of the patients assessed at one year, only 15% had no comorbidity and 25% had a previous history of cancer. Thirty-two (67%) of the enrolled patients were admitted to the ICU after surgery, while 16 (33%) admissions were medical. Nineteen patients (40%) presented an infection at the time of ICU admission. The

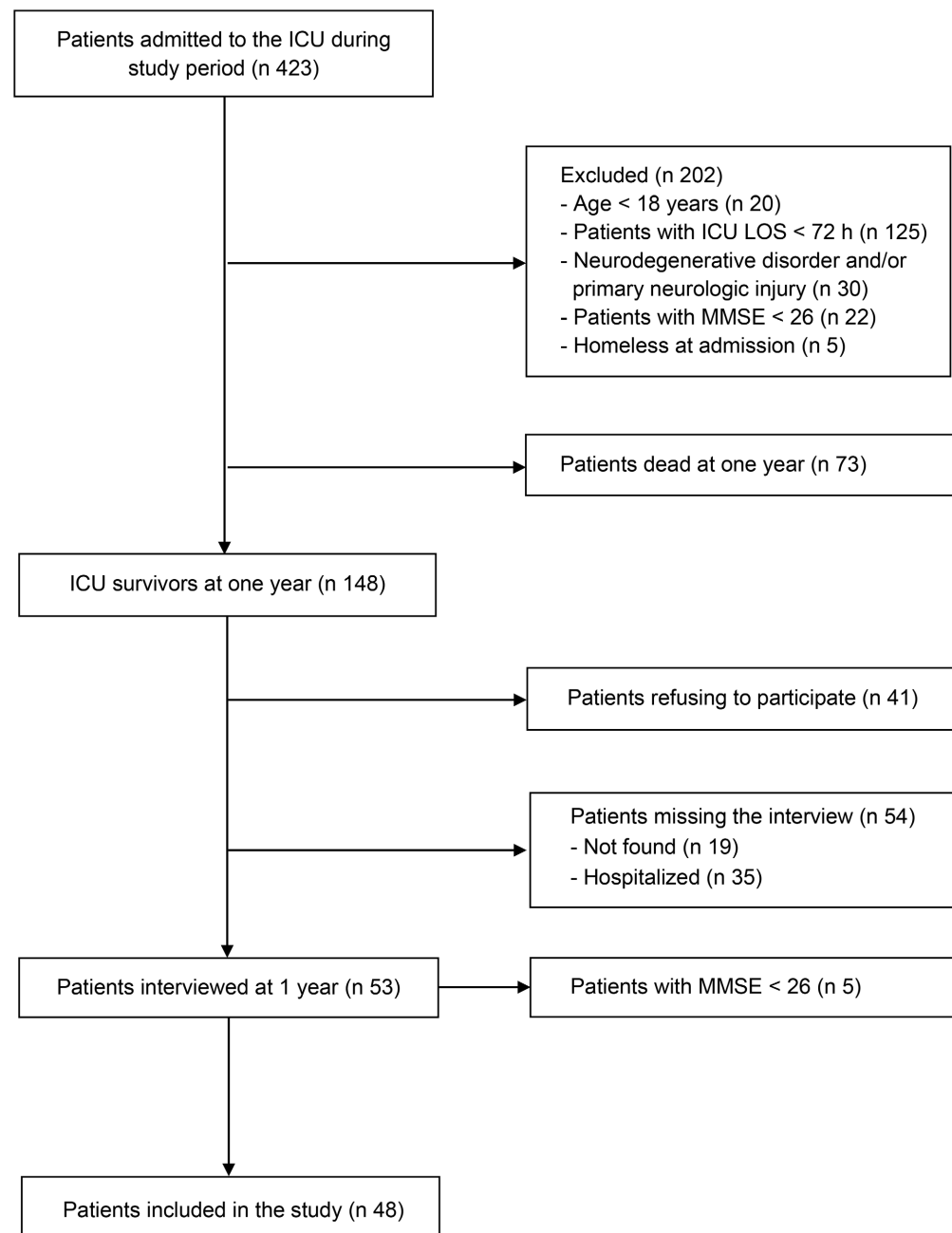


Figure 1. Flow-chart of patient selection.

median values of ICU LOS and hospital LOS were 5.0 [4.0 - 10.0] and 18.0 [13.3 - 32.0], respectively (see **Table 1**).

3.2. GHQ-28 and SF-36

The mean value of the GHQ-28 score in the enrolled patients was 3.98 ± 5.58 (min = 0, max = 24) and the median value was 1.50 (0.25 - 5.0). Cronbach's α for the GHQ-28 was 0.857. In our study population, 14 (29%) patients had a GHQ-28 score greater than or equal to 5. Patients with a GHQ-28 score greater than or equal to 5 were older (mean age 72 ± 10 years) compared to those with a

Table 1. Clinical characteristics of the 48 ICU patients enrolled in the study and comparison between patients with and without psychological impairment.

	Total population n = 48	GHQ-28 < 5 n = 34	GHQ-28 ≥ 5 n = 14	<i>p-value*</i>
Age, years	67 ± 12	65 ± 12	72 ± 10	0.048
Male	34 (71)	26 (77)	8 (57)	0.181
Smokers	16 (33)	12 (35)	4 (29)	0.653
Comorbidities				
Hypertension	27 (56)	19 (56)	8 (57)	0.936
Chronic heart disease	7 (15)	5 (15)	2 (14)	0.970
Diabetes	10 (21)	6 (18)	4 (29)	0.397
Cancer	12 (25)	9 (27)	3 (21)	0.714
Chronic respiratory disease	8 (17)	6 (18)	2 (14)	0.776
Peripheral vascular disease	9 (19)	8 (24)	1 (7)	0.186
Hypothyroidism	3 (6)	1 (3)	2 (14)	0.140
Chronic liver disease	2 (4)	0	2 (14)	0.081
None	7 (15)	5 (15)	2 (14)	0.970
Type of admission				0.822
Medical	16 (33)	11 (32)	5 (36)	
Surgical	32 (67)	23 (68)	9 (64)	
SAPS II score on admission	29 ± 8	28 ± 7	31 ± 10	0.355
SOFA score on admission	3.0 [2.0 - 5.8]	3.0 [2.8 - 5.0]	4.0 [2.0 - 7.0]	0.357
Infection at admission	19 (40)	15 (44)	4 (29)	0.317
Duration of MV, days	2.0 [1.0 - 7.8]	2.0 [1.0 - 5.8]	3.0 [0 - 9.0]	0.639
Duration of sedation, days	2.5 [1.0 - 5.0]	2.0 [1.0 - 5.0]	3.0 [0.8 - 6.5]	0.854
Psychotropic medication in ICU	10 (21)	9 (27)	1 (7)	0.134
ICU LOS (days)	5.0 [4.0 - 10.0]	4.0 [3.8 - 9.3]	6.5 [3.8 - 11.5]	0.505
Hospital LOS (days)	18.0 [13.3 - 32.0]	17.5 [12.8 - 34.5]	19 [13.8 - 30.0]	0.901

*Comparison between groups using Mann-Whitney U tests to compare medians, Unpaired Student's t tests to compare means, or chi-square test to compare proportions. Normally distributed data are shown as mean ± SD; percentage data are shown as *n* (%); not normally distributed data as median [IQR]. SAPS = Simplified Acute Physiology Score; SOFA = Sepsis-related Organ Failure Assessment; MV = mechanical Ventilation; ICU = Intensive Care Unit; LOS = Length of stay.

GHQ-28 score of less than 5 (mean age 65 ± 12 years) (*p* = 0.048), but no statistically significant difference was found between the two groups for the other variables considered (see **Table 1**).

In our total sample, the highest means in the SF-36 eight scales were observed in RE (81.9 ± 33.5) and SF (81.3 ± 26.0), while the lowest means were in the RP

(55.7 ± 37.6) and in GH (61.0 ± 22.5) domains. The means in the two synthetic indices, PCS (43.3 ± 9.3) and MCS (53.4 ± 9.6), were respectively lower and higher than the Italian general population norms [116].

Patients with a GHQ-28 score greater than or equal to 5 one year after ICU discharge had a worse outcome in all the SF-36 domains compared to those with a GHQ-28 score of less than 5 (see **Table 2**). In particular, GH (69.2 ± 16.9 vs. 41.4 ± 22.8 , $p < 0.001$), SF (89.3 ± 16.0 vs. 61.6 ± 34.8 , $p < 0.001$), and RE (93.9 ± 19.5 vs. 51.3 ± 42.2 , $p < 0.001$) were more strongly associated with evidence of psychiatric symptoms. Moreover, we observed a worse health condition in

Table 2. SF-36 data of the 48 ICU patients enrolled in the study and comparison between patients with and without psychological impairment.

	Total population n = 48	GHQ-28 < 5 n = 34	GHQ-28 ≥ 5 n = 14	p-value*
SF-36 items				
Physical Functioning (PF)	69.7 ± 29.4 80 [50 - 95]	77.2 ± 26.8 85 [75 - 95]	51.4 ± 28.1 53 [25 - 75]	0.004
Role-Physical (RP)	55.7 ± 37.6 50 [25 - 100]	64.0 ± 37.0 75 [25 - 100]	35.7 ± 32.1 38 [0 - 75]	0.016
Bodily Pain (BP)	73.7 ± 28.0 84 [56 - 100]	79.5 ± 25.2 84 [70 - 100]	59.7 ± 30.5 57 [41 - 100]	0.024
General Health (GH)	61.0 ± 22.5 67 [50 - 77]	69.2 ± 16.9 72 [62 - 82]	41.4 ± 22.8 33 [25 - 65]	<0.001
Vitality (VT)	71.4 ± 19.8 75 [65 - 88]	77.1 ± 16.3 75 [70 - 90]	57.5 ± 21.1 58 [40 - 70]	0.001
Social Functioning (SF)	81.3 ± 26.0 88 [75 - 100]	89.3 ± 16.0 94 [88 - 100]	61.6 ± 34.8 63 [25 - 100]	<0.001
Role-Emotional (RE)	81.9 ± 33.5 100 [67 - 100]	93.9 ± 19.5 100 [100 - 100]	51.3 ± 42.2 67 [0 - 100]	<0.001
Mental health (MH)	74.4 ± 19.7 76 [64 - 88]	80.0 ± 16.2 84 [72 - 92]	60.9 ± 21.5 62 [40 - 76]	0.001
Physical Component Summary (PCS)	43.3 ± 9.3 45 [38 - 51]	45.7 ± 8.1 47 [42 - 52]	37.4 ± 9.8 38 [29 - 45]	0.005
Mental Component Summary (MCS)	53.4 ± 9.6 56 [48 - 60]	56.6 ± 6.7 59 [53 - 61]	45.4 ± 11.3 47 [37 - 49]	<0.001
Barthel index	97.3 ± 7.1 100 [100 - 100]	98.7 ± 4.1 100 [100 - 100]	94.0 ± 11.0 100 [90 - 100]	0.033

*Comparison between groups using Student's *t*-test to compare means. Data are reported as mean \pm standard deviation (SD) and as median [IQR].

“psychiatric cases” with a GHQ-28 score greater than or equal to 5, which showed limitations in self-care and in physical, social, and role activities (PCS, 45.7 ± 8.1 vs. 37.4 ± 9.8 , $p = 0.005$), and, above all, social and role disability due to emotional problems and psychological distress (MCS, 56.6 ± 6.7 vs. 45.4 ± 11.3 , $p < 0.001$).

3.3. Correlation Analysis

We also investigated a hypothetical association between GHQ-28 total scores and subscales and SF-36 subscales. This analysis highlighted a negative correlation among many domains (see **Table 3**). The GHQ-28 total score and AI and SDep subscales were correlated with all of the eight SF-36 domains, and the SS and SDys subscales were negatively correlated with some SF-36 scales as well (**Table 3**). No correlation was found between the SS subscale and PF, RP, SF, MH, and PCS, and the SDys subscale did not correlate with BP, SF, MH, and MCS (see **Table 3**).

In order to consider the results in our sample with the highest strength of Spearman’s correlation, we chose Spearman’s $\rho > 0.50$ as a cutoff value, suggestive of “moderate correlation” between the variables (with values ranging from -0.50 to -0.70) [117]. A moderate negative correlation was found between the GHQ-28 total score and the RE scale ($\rho = -0.579$, $p < 0.0001$). Moderate negative correlations were also found between the GHQ-28 total score and other SF-36 domains, as follows: RP ($\rho = -0.540$, $p < 0.0001$), GH ($\rho = -0.527$, $p < 0.0001$), VT ($\rho = -0.506$, $p < 0.0001$), and PF ($\rho = -0.501$, $p < 0.0001$). Moderate negative correlations were found between the AI subscale and GH ($\rho = -0.641$, $p < 0.0001$), VT ($\rho = -0.605$, $p < 0.0001$), MH ($\rho = -0.617$, $p < 0.0001$), and RP ($\rho = -0.535$, $p < 0.0001$).

Table 3. Correlations between GHQ-28 and its subscales and SF-36 items.

		PF	RP	BP	GH	VT	SF	RE	MH	PCS	MCS
GHQ-28	ρ	-0.501	-0.540	-0.355	-0.527	-0.506	-0.403	-0.579	-0.485	-0.489	-0.520
	p -value	0.000	0.000	0.013	0.000	0.000	0.004	0.000	0.000	0.001	0.000
SS	ρ	-0.214	-0.230	-0.371	-0.318	-0.310	-0.200	-0.564	-0.254	-0.238	-0.376
	p -value	0.145	0.116	0.009	0.027	0.032	0.173	0.000	0.082	0.112	0.010
AI	ρ	-0.449	-0.535	-0.368	-0.641	-0.605	-0.450	-0.559	-0.617	-0.445	-0.680
	p -value	0.001	0.000	0.010	0.000	0.000	0.001	0.000	0.000	0.002	0.000
SDys	ρ	-0.491	-0.454	-0.251	-0.340	-0.351	-0.273	-0.416	-0.252	-0.448	-0.221
	p -value	0.000	0.001	0.085	0.018	0.015	0.060	0.004	0.084	0.002	0.141
SDep	ρ	-0.506	-0.490	-0.479	-0.508	-0.488	-0.514	-0.519	-0.592	-0.500	-0.538
	p -value	0.000	0.000	0.001	0.000	0.000	0.000	0.000	0.000	0.000	0.000

ρ = Spearman’s rho. GHQ-28 subscales: SS = Somatic Symptoms (subscale A, items 1 - 7); AI = Anxiety and Insomnia (B, 8 - 14); SDys = Social Dysfunction (C, 15 - 21); SDep = Severe Depression (D, 22 - 28). SF-36 items: PF = physical functioning; RP = physical role functioning; BP = bodily pain; GH = general health perceptions; VT = vitality; SF = social role functioning; RE = emotional role functioning; MH = mental health; PCS = physical component summary; MCS = mental component summary.

= -0.535, $p < 0.0001$). Moderate negative correlations were also found between the Sdep subscale and MH ($\rho = -0.592$, $p < 0.0001$), SR ($\rho = -0.514$, $p < 0.0001$), GH ($\rho = -0.508$, $p < 0.0001$) and PF ($\rho = -0.506$, $p < 0.0001$).

Finally, the strongest negative correlation between the two synthetic indices of SF-36 (PCS and MCS) and the GHQ-28 score and its subscales was found between the AI subscale and MCS ($\rho = -0.680$, $p < 0.0001$). Not negligible, concerning possible clinical meaning, were the moderate correlations between the GHQ-28 total score and its subscale Sdep and MCS ($\rho = -0.520$, $p < 0.0001$ and $\rho = -0.538$, $p < 0.0001$, respectively).

Univariate analysis showed that all the SF-36 items (PF, RP, BP, GH, VT, SF, RE, MH) and the physical (PCS) and mental (MCS) component summary were associated with the presence of a GHQ-28 score ≥ 5 . The multivariate analysis showed that RE was the only predictor independently associated with the presence of psychological distress [$p = 0.023$; OR = 0.955; 95% C.I. for OR: 0.917 - 0.994] (see **Table 4**).

4. Discussion

The first result of the present study is that patients screened for psychiatric symptoms had a worse HRQOL compared to those without symptoms. This finding is consistent with previous studies [12] [118] [119]. Almost a third (29%) of our sample could be considered as “psychiatric cases”, having a total GHQ score greater than or equal to 5, and this subgroup consisted of the older subjects (mean age = 72 ± 10 years). This figure shows that psychiatric symptoms were

Table 4. Univariate and multivariate logistic regression.

	Crude OR	95% CI for OR		p -value	Adjusted OR	95% CI for OR		p -value
		Lower	Upper			Lower	Upper	
PF	0.970	0.948	0.993	0.010	0.967	0.931	1.005	0.088
RP	0.979	0.961	0.997	0.023	1.015	0.975	1.057	0.455
BP	0.975	0.952	0.998	0.034	1.029	0.967	1.095	0.365
GH	0.938	0.903	0.974	0.001	0.971	0.916	1.030	0.324
VT	0.945	0.908	0.984	0.005	0.993	0.921	1.070	0.852
SF	0.958	0.930	0.986	0.004	0.982	0.906	1.065	0.659
RE	0.959	0.933	0.985	0.003	0.955	0.917	0.994	0.023
MH	0.948	0.913	0.984	0.005	0.967	0.898	1.042	0.380
PCS	0.902	0.833	0.977	0.011				
MCS	0.863	0.784	0.950	0.003				

SF-36 items: PF = physical functioning; RP = physical role functioning; BP = bodily pain; GH = general health perceptions; VT = vitality; SF = social role functioning; RE = emotional role functioning; MH = mental health; PCS = physical component summary; MCS = mental component summary. OR = odds ratio; CI = confidence interval.

found especially in older ICU survivors among a population of senior subjects (mean age = 67 ± 12 years). In this regard, ageing could be considered to be a significant variable in an ICU survivor being more vulnerable to psychological distress. In previous studies [36] [61] [70] [71] [76], being of younger age was considered a patient-specific risk factor predictor of psychological morbidity following critical illness, but, in those cases, the average age of the subjects was lower than in our sample. It is possible to assume that, in larger samples with a much wider age range, other age-related variables may otherwise affect, in many ways, the vulnerability of subjects.

In our study, 5 out of 53 subjects interviewed (9.4%) were excluded because of a lack of cognitive integrity (MMSE score < 26). Long-term cognitive impairment is another frequent adverse clinical outcome of critical illness and ICU stay, especially in elderly patients [57] [58]: it affects 4% - 78% of ICU survivors from six months to six years post-hospital discharge [66] and involves different cognitive domains, with deficits in memory, attention, and executive function [10]. Sometimes, after certain clinical situations such as acute respiratory distress syndrome or severe sepsis, ICU survivors show moderate or severe cognitive impairments lasting up to 8 - 12 years [59]. This complication often becomes apparent only after ICU discharge, and may improve partially over the first year post-ICU [10] [57] [61]. Among those interviewed in our study 12 months after an ICU stay, almost one-tenth of participants had still not recovered good cognitive functioning, or they showed evidence of an overt cognitive impairment, a finding that may also be due to the high average age of our sample.

Among the ICU survivors, greater impairment of HRQOL in all the SF-36 domains has been found, particularly in those that evaluate social functioning, mental health and wellbeing (SF, RE, MH, VT, and GH). At the same time, an altered GH and an impaired PF, together with BP and limits in RP, also could suggest that the HRQOL of ICU survivors with psychiatric symptoms was negatively affected by the levels of “disability” in performing physical activities of everyday life, and by the limitations in physical, social and role activities. The lowest scores in the two synthetic indices of PCS and MCS could confirm this double component of lower HRQOL in “psychiatric cases” among ICU survivors. As a whole it can be inferred that the quality of life of ICU survivors could be related to the complex interplay of somatic and psychological factors: a more impaired physical functioning could contribute to the development and manifestation of psychological distress; conversely, the patients’ functional disability could be adversely affected by an impaired psychological function. These findings seem to be supported also by data shown by the linear correlations, as follows.

First, the extent of the emotional conditioning over the quality of the performances in daily activities of ICU survivors could depend on the mental condition of the subject. Emotional role functioning, an indicator of the degree of social and individual “disability”, referring to the degree to which the emotional

state limits the work or the overall performance in other daily activities, was more impaired in subjects identified as “cases” ($\text{GHQ-28} \geq 5$). The negative correlations found between RE and the GHQ-28 total score, SS, AI, and SDep highlights the relevance of mental state and of the severity of somatic symptoms, anxiety, insomnia, and depression in conditioning a negative emotional state in ICU survivors, and, consequently, in impairing HRQOL in the performance of daily life activities. ICU survivors with psychiatric symptoms are those who, for emotional reasons, show more difficulties in work and in other daily activities. Conversely, we have also to consider how much a negative emotional state could affect the presence of psychiatric symptoms. Our univariable analysis showed that the presence of psychological distress was explained by all SF-36 items. Interestingly, in the multivariable analysis, the only item significantly associated with impaired mental functioning was the emotional role functioning RE ($p = 0.023$; $\text{OR} = 0.955$; 95% C.I. for OR: 0.917 - 0.994). This finding describes how the limitation in one’s job or in other daily activities due to the emotional state has a major impact on the development of psychiatric symptoms in our study population independently from the other limitation in HRQOL.

Second, the negative correlations between the GHQ 28 total score and the SF-36 domains evaluating physical wellbeing (PF, RP, GH, and VT) emphasize the bidirectional relationship between physical impairment and mental health mentioned above. The finding that “psychiatric cases” among ICU survivors have more impaired physical functioning suggests the role played by this issue in negatively affecting the individual HRQOL in these patients and in contributing to the development and manifestation of psychiatric symptoms.

Third, in our study, it seems that anxiety and insomnia (AI) could be particularly involved in the impairment of the HRQOL of ICU survivors, affecting different health dimensions such as the impact of the emotional state on personal performances in daily activities (RE), the subjective view and evaluation of one’s own health (GH), and perceived personal vitality (VT). Psychological distress, social functioning, and mental health in ICU survivors could be therefore particularly affected by the presence of AI. At the same time, we cannot exclude that the physical complications and the patient’s functional disabilities detected after an ICU stay themselves might implicate a negative evaluation of one’s own health (GH), a reduced perceived personal vitality (VT) and role limitations (RP), conditions that could trigger psychiatric symptoms, particularly AI.

Fourth, the negative correlations found between the SDep GHQ-28 subscale and several QOL domains, such as MH, SF, GH, and PF, could indicate a link between the severity of depressive symptoms and the degree of impairment of mental functioning, with regard to emotional and behavioral aspects and in personal attitudes toward life, the degree of impairment of social activities, an altered perception of one’s own health, and functional impairment in physical abilities. Therefore, the depressive component too could be a particularly critical factor related to the impairment of HRQOL in ICU survivors at 12 months after

discharge.

Finally, correlations between the GHQ-28 total scores, AI, and SDep subscales, and the SF-36's MCS are to be expected, confirming the relevance of psychiatric symptoms in impairing HRQOL in domains related to the general state of mental health and to the degree of social functioning.

In order to understand the reasons for the negative correlation between GHQ 28 total score and the scores in the different SF-36 domains, it is necessary to consider the structure of the two scales: the GHQ-28 total score increases with the severity of the impairment of physical and psychological health, whereas the SF-36 score decreases in relation to the severity of the impairment in its different domains. We have also to take into account that, as mentioned earlier, there are areas of overlap between the GHQ-28 subscales and some dimensions of the SF-36: the GHQ-28 assesses the overall degree of psychological health and the SF-36 domains evaluate aspects of the quality of life that contribute to defining the degree of psychological well-being. Our findings are in line with other studies that found significant negative associations between psychiatric symptoms and quality of life in ICU survivors [70].

Furthermore, despite the 12-months time period considered in our study, there could be the effect of an incomplete physical recovery after staying in the ICU, thus justifying lower SF-36 scores and greater psychological distress with higher GHQ-28 scores in ICU survivors. It is well known that severe illness and treatment in an intensive care unit may cause significant physical sequelae, such as severe weakness, with a significant impact “on the pace and degree of recovery and return to the former functional status of patients”, thus compromising the quality of life and mental health [120] [121].

In addition, we have to consider that almost 1/3 of the patients in our sample were “psychiatric cases” with a GHQ-28 score ≥ 5 , that they had a worse outcome in all SF-36 domains and that they were older than those with a GHQ-28 score < 5 . Ageing could therefore be considered a factor that negatively affects HRQOL and makes it more vulnerable to psychological distress. Also from this point of view, one could better understand the finding of the negative correlation between the GHQ 28 total score and the SF-36 domains.

5. Limitations of the Study

This study has several limitations and possible sources of bias.

First of all, we have to consider the inevitable lack of assessment with standardized criteria for mental health and HRQOL of the subjects before ICU admission. Retrospective measurement of mental health status or perceived quality of life may introduce a recall bias, since preadmission status is often difficult to be obtained directly in the ICU setting [122]. In addition, data concerning the previous quality of life retrieved indirectly by close relatives might not always demonstrate a close agreement with the patients' opinions [97]. Critical illness and ICU stay could trigger negative emotional reactions, psychiatric morbidity,

cognitive impairment and impairment in HRQOL in particularly vulnerable patients [29] [72] [73]. Furthermore, several findings show that low HRQOL before ICU admission, compared to that of the general population, correlates with a poor outcome [11] [64] [113] [123] [124] [125], so that an impaired HRQOL after ICU may reflect a poor baseline situation rather than being a consequence of intensive care [2].

Another limitation of our study is the lack of evaluation of cases of delirium during an ICU stay [13] [18], so it was not possible to take into account the impact of severity and duration of delirium on adverse psychological outcomes [10] [38] [58] [66] [126].

Due to the tools used in this study, another limit is the lack of clinical diagnosis of the mental health of the participants. GHQ-28 subscales were correlated to the SF-36 domains without allowing for exploration of any correlations of the SF-36 domains with specific psychiatric diagnostic categories, like, for example, post-traumatic stress disorder and depression, which previous studies have shown to play an important role in impairing the HRQOL in ICU survivors [70] [118] [127] [128].

Finally, we should not ignore the limits of generalization related to the small size of the study's sample, as a whole as well as in the two subgroups defined according to the GHQ-28 cutoff value. It would be useful for future research to carry out similar studies on a wider scale in order to deal with this issue in a more appropriate manner.

6. Conclusions

To our knowledge, this study is the first to assess the presence of psychiatric symptoms through GHQ-28 questionnaire in an Italian ICU survivor's population and it is the first one to investigate correlations between psychological distress and HRQOL in ICU survivors using the GHQ-28 survey as a screening tool. Despite referring to a very limited population, these data could be a useful reference for future studies in the critical illness setting.

Psychiatric symptoms and cognitive impairment were found at considerable rates in our study. The use of quick and easy administered screening tools like MMSE and GHQ-28 could help clinicians, first of all, General Practitioners, to identify patients in need of specific care for neuropsychiatric sequelae after ICU stay. This issue seems to be particularly relevant for older ICU survivors, in which several age-related variables coexist and influence their vulnerability to psychological distress, cognitive impairment and social disadvantage. Furthermore, psychiatric comorbidity in ICU survivors seems to be associated with the impairment of HRQOL, particularly in domains related to social functioning, to the subjective perspective of one's own health, to perceived personal vitality, and to the role of emotional states in limiting the performance of work and other daily activities. Also, physical functioning seems to be particularly involved in the greater impairment of HRQOL in ICU survivors with psychiatric symptoms.

Difficulties in performing activities of daily life could trigger significant psychological distress in ICU survivors and, conversely, they could be negatively affected by the psychological condition.

We think that these findings could contribute to stress the clinical relevance of the relationship between the psychological condition of ICU survivors and specific aspects of their HRQOL one year after ICU discharge. For this reason, long-term follow-up of patients after a critical illness is necessary, monitoring mental state along with physical condition and ensuring continuity and appropriateness in the therapeutic intervention. Similarly, it would be necessary to plan regular assessments of psychological outcomes in family members of ICU survivors, who are often burdened by their caregiving role and at high risk for adverse psychological outcomes and psychiatric morbidity.

The focus on follow-up and treatment of psychiatric symptoms is even more important if we consider the extent to which Emotional State, a specific domain of HRQOL, can limit the performance in daily activities of these patients. As our study showed, depression, anxiety and insomnia are particularly involved in the impairment of HRQOL of ICU survivors. A specific intervention may help to improve social functioning and ICU survivors' HRQOL in domains related to mental health status. The interplay between somatic and psychological factors in determining a lower HRQOL among ICU survivors requires multimodal interventions on impaired physical functioning and psychological distress, such as personalized therapies, rehabilitation programs, psychotropic medications, support groups, psycho-educational and psychotherapeutic treatments.

Ethics

All procedures performed in the study were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards were approved by the Ethical Committee of Province of Ferrara (Italy)—Reference Number: 140696. All patients took part on a voluntary basis and were not remunerated for their participation. They were given assurance of anonymity and confidentiality of the information provided and were informed that they could stop completing the questionnaire at any time if they wished. They were also assured that the collected data would be used only for the purpose of the study and that their decision to withdraw would not compromise the standards of the care provided.

Informed Consent

Signed informed consent was obtained from all research participants.

Authors' Contributions

All authors contributed significantly to the study's conception and design. Stefano Tugnoli carried out the interviews, collaborated with the implementation of

the research project, and was responsible for the data collection/handling, for the review of the literature and for the drafting of the manuscript. Savino Spadaro planned the research project, contributed to its implementation and the data analysis, and revised the manuscript. Francesca Dalla Corte contributed to the preparation of the manuscript and the data analysis. Giorgia Valpiani was responsible for the data analysis. Carlo Alberto Volta and Stefano Caracciolo supervised the design of the study and critically reviewed the manuscript, giving final approval for submission.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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