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Quality of life of the mechanically ventilated patients with community-acquired pneumonia

Kvalitet života posle mehaničke ventilacije kod bolesnika lečenih od pneumonije

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Abstract

Background/Aim. Patients with pneumonia who require mechanical ventilation (MV) are associated with several poor outcomes such as prolonged hospitalization, higher rate of mortality and increased spread of antibiotics-resistant pathogens. MV in patients with community-acquired pneumonia (CAP) could cause development of psychological symptoms, often neglected in the Intensive Care Units (ICU) as well as decreased quality of life after the withdrawal of the MV. The aim of the study was to evaluate the quality of life in patients with CAPs treated with MV in ICU. **Methods.** The study was designed as a cohort study of hospital-treated patients with CAP with prospective data collection. The quality of life was defined as the primary outcome, while the use of MV was assumed as the primary prognostic factor that adversely affected the outcome. The patients were recruited from the population of patients with CAPs who were hospitalized at the ICU, Clinical Center Kragujevac, Serbia, from January 2013 to January 2014. The experimental group consisted of patients who were on MV while the control group included patients who were treated for CPAs in the ICU, but were not subjected to MV. The quality of life was assessed by using patient-rated Euro Quality of Life (EuroQoL) Group-EQ-5D index. The calculation of the total EQ-5D-5L score values was performed by using the predefined, validated mapping key according to response combinations. Statistical analysis was performed by using χ^2 test, Student's *t*-test, univariate and multivariate logistic regression analyses. **Results.** The patients with MV had worse EQ5D-5L values in comparison to the control group for all 5 domains. Mobility, self-care and usual activities were negatively affected during the whole follow-up period. Pain or discomfort and anxiety or depression differed significantly between the study group and the control group at days 7 and 30. **Conclusion.** Patients with MV tend to have poorer quality of life, especially in 3 domains. The main reasons are the presence of chronic comorbidities in the population that require MV.

Key words:
respiration, artificial; pneumonia; critical care; quality of life; prognosis.

Apstrakt

Uvod/Cilj. Bolesnici sa pneumonijom koji zahtevaju mehaničku ventilaciju (MV) povezani su sa nekoliko loših ishoda, kao što su produžena hospitalizacija, veća stopa smrtnosti i povećano širenje patogena otpornih na antibiotike. MV kod bolesnika sa vanbolnički stečenom pneumonijom (*community-acquired pneumonia* – CAP) može izazvati razvoj psihološke simptomatologije, koje su često zanemarene u jedinicama intenzivnog lečanja (JIL), i smanjenjem kvaliteta života nakon prestanka MV. Cilj studije je bio da se proceni kvalitet života kod bolesnika sa CAP koji se leče primenom MV u JIL. **Metode.** Istraživanje je sprovedeno u obliku studije koja je obuhvatala hospitalizovane zbog CAP. Kvalitet života definisan je kao primarni ishod, dok je primena MV pretpostavljena kao primarni prognostički

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faktor koji negativno utiče na ishod. Bolesnici su regrutovani iz populacije bolesnika sa CAP koje su bile hospitalizovane u JIL u Kliničkom centru Kragujevac, Srbija, od januara 2013. do januara 2014. godine. Eksperimentalna grupa sastojala se od bolesnika koji su bili na MV, a kontrolna grupa bili su bolesnici sa CAP, kiji nisu bili podvrgnuti MV. Kvalitet života procenjen je pomoću EuroQoL Group-EQ-5D indeksa. Izračunavanje ukupne vrednosti EQ-5D-5L izvršeno je korišćenjem unapred definisanog, validiranog kartografskog ključa, u skladu sa kombinacijama odgovora. Statistička analiza obavljena je korišćenjem χ^2 testa, Studentovog *t*-testa, univarijantne i multivariantne logističke regresione analize. **Rezultati.** Bolesnici sa MV imali su lošije vrednosti EQ5D-5L u poređenju sa kontrolnom grupom za svih pet domena. Mobilnost, samozbrinjavanje i uobičajene aktivnosti bili su najlošije ocenjeni tokom čitavog perioda praćenja. Bol ili neugodnost i anksioznost ili depresija značajno su se razlikovali između studijske i kontrolne grupe u sedmom i tridesetom danu lečenja. **Zaključak.** Bolesnici sa MV imaju slabiji kvalitet života, naročito u tri domena. Glavni razlozi su prisustvo hroničnih komorbiditeta kod populacije koja zahteva primenu MV.

Ključne reči:
disanje, mehaničko; pneumonija; intenzivna nega; kvalitet života; prognoza.

Introduction

Community-acquired pneumonia (CAP) represents acute infection of lung parenchyma, associated with systemic of inflammatory response and with the presence of infiltrations on chest radiography in patients who were not hospitalized in the last 14 days before the onset of symptoms [1]. CAP is a frequent disease encompassing all ages, being more prevalent in patients with associated co-morbidities particularly chronic obstructive pulmonary disease (COPD), chronic heart failure (CHF), chronic liver and kidney diseases, Alzheimer's dementia, cystic fibrosis (CF), immunocompromised syndromes and in those who are smokers [2]. Approximately 0.5%–1% of people from the adult population are diagnosed with some form of CAP annually. Among them, 22%–42% need hospitalization, out of which 5% to 10% need to be treated in the intensive care unit (ICU) [3, 4].

Patients with pneumonia who require the mechanical ventilation (MV) treatment are at the increased risk for several poor outcomes such as prolonged hospitalization and colonization with pathogens resistant to antibiotics as well as a higher mortality rate [4]. In addition, the mechanically ventilated patients with CAP frequently develop central nervous system disturbances which could adversely affect the quality of life of survivors [5, 6]. The quality of life, as defined by the World Health Organization, is "the individual perception of their life position, in the context of culture and system values in which they live and in relation to their goals, standards, expectations and concerns." It estimates the gap between the expectations of people and their achievements and it reflects the satisfaction of the individual to his/her whole life [7].

Despite the high medical and economic burden imposed on societies throughout the world, the studies reporting its influence on the quality of life of the survivors are not common [8–11]. Initial studies investigated the quality of life of CAP patients mostly as a secondary outcome giving limited data about it such as the baseline values and the change trends during the course of the treatment [12]. In these times, researches revealed connections between pneumonia and disturbances of systemic homeostatic pathways on molecular levels (e.g., cytokine response), but their consequences on the quality of life were poorly understood [13, 14]. The interest for the topic has recently been raised, and in studies which appeared it was found that physical components, mobility, self-care and usual activities were the most affected domains of the quality of life of the patients recovering from pneumonia [15, 16]. In addition, our knowledge about the underlying biological mechanism of the poor quality of life is increasing rapidly, including the role of mediators of acute inflammation [17].

However, very little is known about the quality of life parameters within various clinical types of the disease in various patient population such as community-acquired, nosocomial and pneumonia treated in the intensive care units. There is a need for increasing our knowledge about the role of proposed predictors of poor quality of life outcomes including their influence within separate patients' subgroups by using different treatment strategies.

Therefore, we hypothesized that the MV represented the independent risk factor for the decreased quality of life of the patents who recovered after community-acquired pneumonia. In this study, we aimed to estimate the quality of life of the patients with CAP who were on MV, compared to those with CAP who were not on MV.

Methods

The research was designed as a cohort study in the hospital-treated patients with CAP and prospective data collection. The quality of life was considered as the primary outcome, while the use of MV was assumed as the primary prognostic factor that adversely affected the outcome. The quality of life was followed repeatedly according to the dynamics of the expected recovery from pneumonia in the course of three study visits.

Study population

Patients were recruited from the population of patients with CAP who were hospitalized in the Emergency Center, Intensive Care Unit, Clinic for Pulmonology and Clinic for Infectious Disease of the Clinical Center "Kragujevac", Kragujevac, Serbia, from January 2013 to January 2014. The experimental group consisted of patients who were treated and

mechanically ventilated while the control group were patients who were treated, but were not mechanically ventilated. The inclusion criteria were the following: female or male adults (≥ 18 years), patients who had CAP confirmed by microbiological, radiographic and laboratory tests, and those who gave voluntary informed consent for the participation in the study. The patients were excluded from the study if they had been mechanically ventilated more than 24 hours before their admission to the hospital, if they were mechanically ventilated for a disease other than CAP, pregnant and lactating women, patients from whom we could not get accurate data needed for the research at baseline (e.g., psychiatric patients with altered cognitive functions, patients with incomplete data in the available medical records patients for whom the adequate monitoring by the end of the study was unlikely at the time of screening) and patients who refused to give informed consent.

Only those patients who survived to the day 90 after MV stopping (experimental group) and their controls (matching the time of hospital stay) with the same period of surviving, were included in the study.

In total, there were 164 patients eligible for study participation at the screening time, but 17 (10.3%) of them refused to give their informed consent and therefore 147 (89.7%) patients were included in the study. During the study period, the fatal outcome was confirmed in 3 (2%) patients and 14 (9.5%) patients were lost to follow-up and they did not complete all study visits. Therefore, the data from 130 patients who completed all three study visits were included in the analysis. A total of 65 patients were treated in ICU (all subjects were in the experimental group), 21 subjects were treated in the semi-ICU and 44 patients were treated in the clinical wards.

Study variables

We measured the quality of life by using patient-rated Euro Quality of Life (QoL) Group-EQ-5D index [18]. It consisted of two parts: five domains (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and visual analog scale (VAS). The new version of the EQ-5D used in the study included five grading levels, in each of the five EQ-5D domains and it is called EQ-5D-5L. The calculation of the total EQ-5D-5L score value, according to response combinations, was performed by using the predefined, validated mapping key. Clinical, laboratory and socio-demographic data were considered as secondary variables.

Data collection

Baseline visit was done at the index day. For the experimental group, the index day was day 7 after stopping MV. For the control group, the index day was within the period of 7 days from his or her matching subject's index day in the experimental group. All study patients were in hospital at the baseline visit. The researchers retrieved in detail the patients' medical files and collected necessary data. At the same time, the patients were interviewed for EQ-5D-5L questionnaire data collection. The second visit was performed on day 30 after the baseline (index day). At the second visit, all study patients were discharged from hospital and were at their homes. Therefore, EQ-5D-5L data collection was performed during a phone interview through asking and answering the question-by-question. In addition, the researchers asked the patients if the significant changes in their comorbid disease (including drug treatment) had appeared since the time of their hospital stay. The third visit was performed on day 90 after the index day and the researchers collected data using the same approach as for the second visit.

Statistical analysis

We performed sample size calculation based on a presumed level of the mean of weighted EQ-5D-5L total index of 0.7, standard deviation of 0.2 and the difference of at least 15% between the study arms, presuming the poorer scores in the mechanically ventilated patients. The difference was considered clinically significant based on the quality of life estimations of patients with asthma or COPD of different severity types as the appropriate data in the patients with CAP or other types of pneumonia, using EQ-5D, at the time of designing our study were scarce [19]. According to these presumptions, alpha error of 0.05, study power of 0.8 and allocation ratio of 1:1, we calculated the sample size of at least 130 patients, 65 in each study group [20]. Data were analyzed by descriptive and analytical statistics. We also used χ^2 test and *t*-test for the analysis of influence of different demographic, clinical, laboratory factors between the compared groups. All data were expressed as means ± standard deviation or frequencies (percentages). Univariate and multivariate linear regression analyses were performed to characterize predictors associated with the total score of EQ-5D-5L. The factors that were present only during the treatment in hospital and whose influence, in terms of biological sense, could not be extrapolated to the days 30 and 90, were not analyzed in univariate or in a multivariable linear regression model. The probability level of significance was $p \leq 0.05$, with two-tailed approach.

Results

The study population consisted of 130 patients who were divided into two groups, 65 patients each. Both groups had similar socio-demographic and clinical characteristics (Table 1). Only marital status and previous surgeries significantly differed between the study groups.

The distribution of comorbidities among patients, who were mechanically ventilated and those who were not, was unequal. Significant differences were observed in the presence/absence of cardiomyopathy, cerebrovascular diseases, chronic kidney disease, hypertension and pulmonary emphysema (Table 2). Among the study population, the use of enoxaparin, spironolactone, carvedilol, amlodipine, methylprednisolone, salbutamol and aminophylline was significantly more frequent in patients who were mechanically ventilated, while angiotensin converting enzyme (ACE) in-

hibitors, amoxicillin and azithromycin were more frequent in the control group (Table 3). Regarding the findings of blood and serum biochemistry [the mean number of erythrocytes and leukocytes and the mean values of hematocrit, platelets, activated partial thromboplastin time (aPTT), creatinine, urea, C-reactive protein, procalcitonin, sodium, potassium, calcium, partial pressure of oxygen, carbondioxide and bicorbonate (pO_2, pCO_2 and HCO_3^-)], only platelet count was significantly higher in patients who were on MV, whereas glycemia was significantly higher in the control group.

Table 1

Demographic and social characteristics of study population

Variable	Experimental group (n = 65)	Control group (n = 65)	*p**
Age (years), mean ± SD	55.6 ± 14.7	42.6 ± 17.4	1.000[a]
Gender, n (%)			
male	32 (49.2%)	37 (56.9%)	0.380[b]
female	33 (50.8%)	28 (43.1%)	
Smoking, n (%)	22 (33.8%)	44 (67.7%)	0.852[b]
Education, n (%)			
elementary school	3 (4.6%)	5 (7.7%)	
high-school	46 (70.8%)	41 (63.1%)	0.804[b]
faculty	16 (24.6%)	19 (29.2%)	
Marital status, n (%)			
single	24 (36.9%)	7 (10.8%)	0.003[b]
married	34 (52.3%)	51 (78.5%)	
divorced	5 (7.7%)	5 (7.7%)	
widow/widower	2 (3.1%)	2 (3.1%)	
Employment status, n (%)			
unemployed	12 (18.5%)	8 (18.5%)	0.076[b]
employed	40 (61.5%)	36 (55.4%)	
student	5 (7.7%)	2 (3.1%)	
retirement	8 (12.3%)	19 (29.2%)	
Material status, n (%)			
good	33 (50.8%)	30 (46.2%)	0.845[b]
moderate	29 (44.6%)	33 (50.8%)	
bad	2 (3.1%)	2 (3.1%)	
excellent	1 (1.5%)	0 (0%)	
Alcohol intake, n (%)	34 (52.3%)	38 (58.5%)	0.480[b]
Allergies, n (%)			
no	44 (67.7%)	45 (69.2%)	
food allergy	21 (32.3%)	17 (26.2%)	0.200[b]
drug allergies	0 (0%)	3 (4.6%)	
Previous surgery, n (%)	36 (55.4%)	52 (80%)	0.003[b]

***p* – probability of a) – independent sample *t*-test or b) – χ^2 test; SD – standard deviation.**

Table 2

Underlying disease and comorbidities

Variable	Experimental group (n = 65)	Control group (n = 65)	*p**
	n (%)	n (%)	
Cardiomyopathy	26 (40.0)	15 (23.1)	0.038
Cerebrovascular disease	14 (21.5)	3 (4.6)	0.004
Liver disease	14 (21.5)	8 (12.3)	0.160
Chronic kidney disease	18 (27.7)	5 (7.7)	0.003
Diabetes mellitus 1	10 (15.4)	4 (6.2)	0.090
Diabetes mellitus 2	10 (15.4)	2 (3.1)	0.015
Bronchopneumonia	39 (60.0)	30 (46.2)	0.114
Lobar pneumonia	26 (40.0)	31 (47.7)	0.377
Severe influenza	5 (7.7)	10 (15.4)	0.170
COPD	15 (23.1)	10 (15.4)	0.266
Arterial hypertension	19 (29.2)	8 (12.3)	0.017
Pulmonary emphysema	14 (21.5)	5 (7.7)	0.025
Arrhythmias	9 (13.8)	3 (4.6)	0.069
Sepsis	1 (1.5)	4 (6.2)	0.171

***p* – probability of χ^2 test; COPD – chronic obstructive pulmonary disease.**

Table 3

The drugs with significantly different frequency of the prescription between study subgroups

Drug	Experimental group, (n = 65) n (%)	Control group, (n = 65) n (%)	*p*
Enoxaparin	12 (18.8)	3 (4.6)	0.015
Spironolactone	17 (26.6)	4 (6.2)	0.002
Carvedilol	19 (29.7)	8 (12.3)	0.015
Amlodipine	25 (39.1)	7 (10.8)	< 0.001
ACE inhibitors	16 (25.4)	58 (89.2)	0.031
Methylprednisolone	31 (47.7)	8 (12.3)	< 0.001
Amoxicillin	2 (3.1)	10 (15.4)	0.015
Azithromycin	15 (23.1)	26 (40)	0.038
Salbutamol	31 (47.7)	16 (24.6)	0.006
Aminophylline	27 (41.5)	11 (16.9)	0.002

***p* – probability of χ^2 test; ACE – angiotensin converting enzyme.**

The mechanically ventilated patients had worse EQ5D-5L values in comparison to the control group for all 5 domains. Mobility, self-care and usual activities were negatively affected over the whole follow-up period (on days 7, 30 and 90) (Figures 1, 2 and 3); pain/discomfort and anxiety/depression differed significantly between the study and the group on days 7 and 30 (Figures 4 and 5).

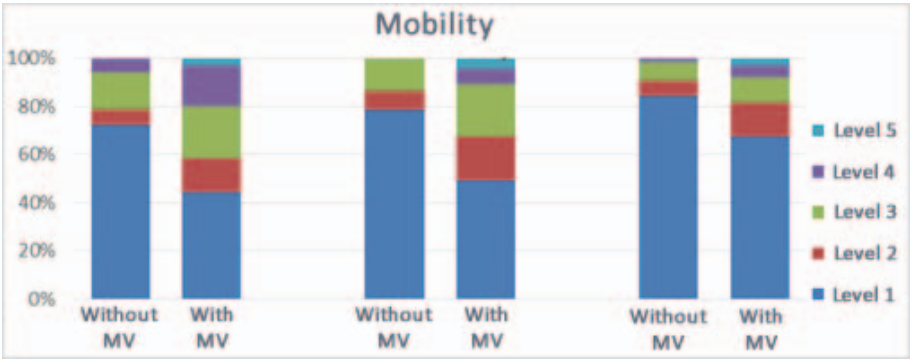

Fig. 1 – EQ-5D values for mobility domain.
MV – mechanical ventilation.

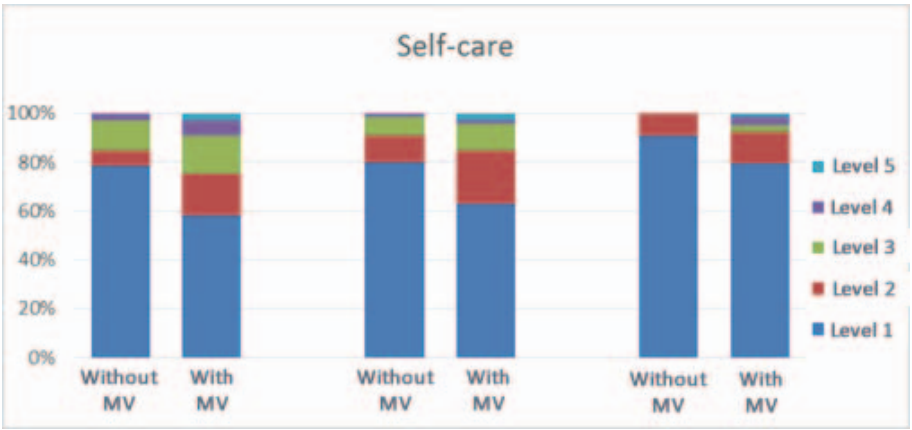

Fig. 2 – EQ-5D values for self-care domain.
MV – mechanical ventilation.

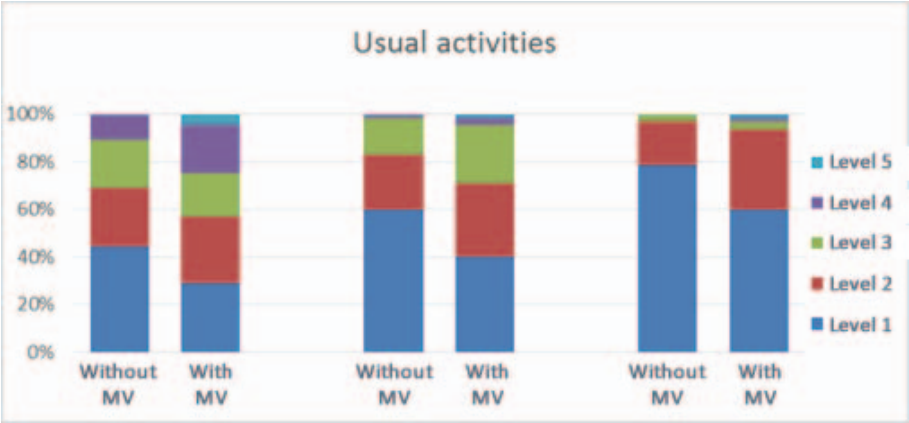

Fig. 3 – EQ-5D values for usual activities domain.
MV – mechanical ventilation.

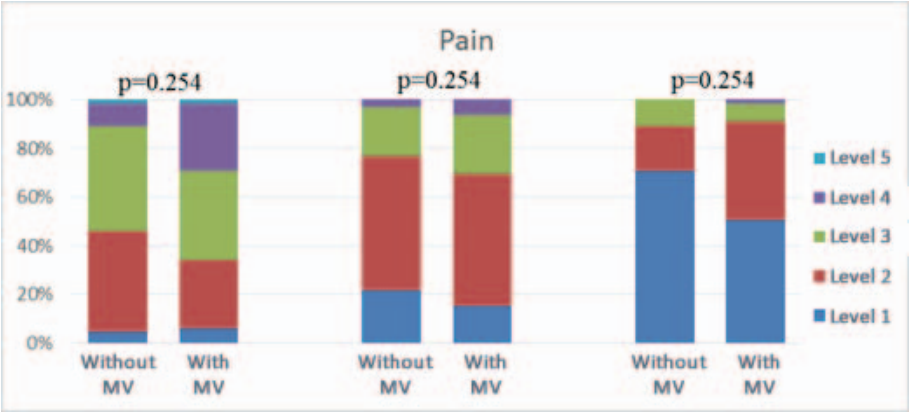

Fig. 4 – EQ-5D values for pain domain.
MV – mechanical ventilation.

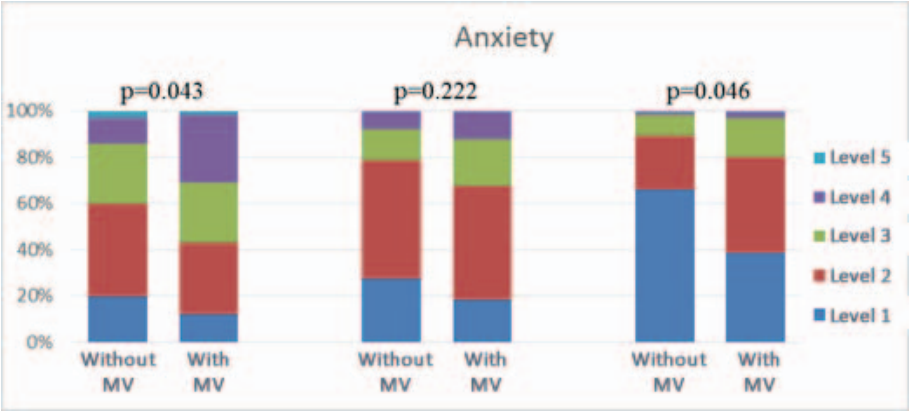

Fig. 5 – EQ-5D values for anxiety domain.
MV – mechanical ventilation.

Average values of EQ-5D VAS scores in patients who were mechanically ventilated during the study period are listed in the table (Table 4). Statistically significant differences in the mean values of EQ-5D VAS scores between the groups were after 7 days ($p = 0.003$), after 30 days ($p = 0.004$) and after 90 days ($p = 0.001$).

Overall, for both groups, there was a significant change in the values of EQ-5D VAS scores in time ($F = 411.406$, $p < 0.001$). There was a significant increase in the value of EQ-5D VAS during the study period (Figure 6). Generally, in the reporting period, there was a statistically significant difference in the values of EQ – 5D VAS scores between groups ($F = 10.010$, $p = 0.002$). There were no significant interactions between the groups and changes in the value of EQ-5D VAS scores during the study period ($F = 0.691$; $p = 0.450$).

Average values of EQ-5D index in the mechanically ventilated patients during the study period are listed in Table 4. Statistically significant differences in mean values of EQ-5D index between the examined groups were noted after 7 days ($p = 0.004$), after 30 days ($p = 0.011$) and after 90 days ($p = 0.003$). Overall, there was a statistically significant

change in the value of EQ-5D index in time (F = 92.598, $p < 0.001$) for both groups. There was a significant increase in the values of the EQ-5D index during the study period (Figure 7). Overall, in the reporting period, there was a significant difference in the values of EQ-5D index (F = 10.027, $p = 0.002$) between the groups. There were no significant interactions between the groups and changes in the values of EQ-5D index during the study period (F = 0.423; $p = 0.621$).

Table 4

The values of EQ-5D VAS domain and EQ-5D index domain in patients with and without mechanical ventilation

Day	Mechanical ventilation	EQ-5DVAS mean ± SD; median (range)	*p*	EQ-5DVAS mean ± SD; median (range)	*p*
7	No	68.4 ± 17.9; 70.0 (20.0–92.0)	0.003	0.70 ± 0.23; 0.78 (0.01–1.00)	0.004
	Yes	58.7 ± 18.2; 60.0 (20.0–90.0)		0.57 ± 0.28; 0.57 (0.05–1.00)	
30	No	76.8 ± 16.0; 80.0 (35.0–100.0)	0.004	0.79 ± 0.19; 0.86 (0.20–1.00)	0.011
	Yes	68.3 ± 17.0; 70 (20.0–95.0)		0.68 ± 0.27; 0.76 (-0.43–1.00)	
90	No	84.7 ± 14.4; 90.0 (45.0–100)	0.001	0.91 ± 0.14; 1.00 (0.54–1.00)	0.003
	Yes	76.0 ± 16.0; 80.0 (30.0–100)		0.80 ± 0.25; 0.86 (0.29–1.00)	

VAS – visual analogue scale; SD-standard deviation.

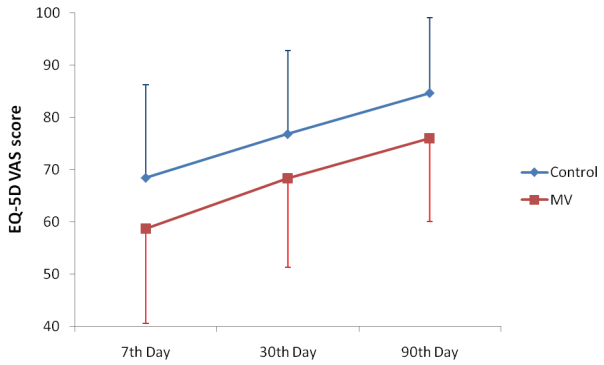

Fig. 6 – EQ-5D VAS scores in the mechanically ventilated (MV) and control group of patients. The points and the vertical bars represent the medians and the interquartile ranges, respectively.
VAS – visual analog scale.

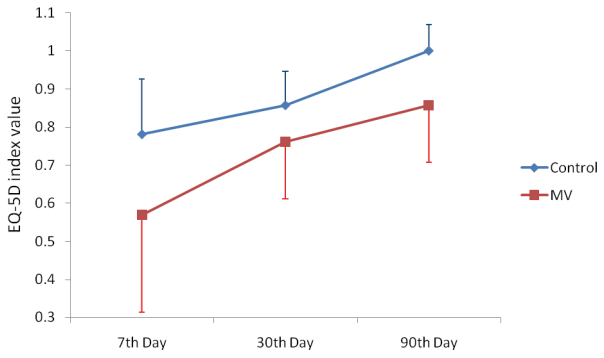

Fig. 7 – EQ-5D index values in the mechanically ventilated (MV) and control group of patients. The points and the vertical bars represent the medians and the interquartile ranges, respectively.

Using univariate linear regression model with the values of the total scores of EQ-5D index on days 7, 30 and 90 being dependent variables (outcome), we found that 15 variables (from the total number of 25 analyzed) were significantly associated with lower values of the EQ-5D index scores, at least at one time, indicating worse quality of life (Table 5). However, no variable consistently influenced the quality of life across all study visits, and, in general, the magnitudes of their effects were mostly mild. In three models of multivariate linear regression (corresponding to three study visits), only age was significantly associated with lower scores of EQ-5D-5L index over two visits. The presence of diabetes mellitus type 1, chronic kidney disease and the use of amlodipine and methylprednisolone were also significant predictors of lower quality of life scores, but their influences were time-limited. Bearing in mind the possibility of indirect associations and other indirect impacts (confounding factors), the impact of variables that were statistically significant was further analyzed by multivariable linear regression models.

The factors that were present only during the treatment in hospital and whose influence, in terms of biological sense, cannot be extrapolated to days 30 and 90, were not analyzed it in this or in a multivariable linear regression model. Approximately, it was assumed that the use of amlodipine, ACE inhibitors and aminophylline was used during the whole period for the treatment of hypertension and pulmonary obstruction, while the impact of methylprednisolone was limited to the first 7 days, while chronic use of oral corticosteroids was not used for such a long period. Therefore, only these four drugs were taken for the multivariate model (Table 6). In addition, the impact of pO_2 and pCO_2 outside the acute treatment period was also unlikely, so they were excluded from this table for days 30 and 90 and from a multivariate model.

Table 5

Variables significantly associated with a total score of EQ-5D in the model of univariate linear regression

Variables	7th day		30th day		90th day	
	B	*p*	B	*p*	B	*p*
Mechanical ventilation	-0.132	0.004	-0.105	0.011	-0.109	0.003
Gender	0.028	0.549	0.014	0.734	0.002	0.960
Age	-0.005	< 0.001	-0.005	< 0.001	-0.004	< 0.001
Previous surgery	-0.122	0.014	-0.123	0.005	-0.075	0.055
Cardiomyopathy	-0.005	0.916	-0.086	0.056	-0.113	0.004
Cerebrovascular disease	-0.073	0.295	-0.123	0.047	-0.107	0.050
Chronic kidney disease	-0.141	0.021	-0.191	< 0.001	-0.131	0.006
Hypertension	-0.133	0.021	-0.105	0.040	-0.080	0.079
Diabetes mellitus type 1	-0.177	0.018	-0.118	0.078	-0.083	0.165
Amlodipine	-0.229	< 0.001	-0.115	0.018	-0.116	0.006
ACE inhibitors	-0.126	0.041	-0.083	0.132	-0.093	0.055
Enoxaparin	-0.132	0.073	-0.239	< 0.001	n.a.	
Azithromycin	0.063	0.213	0.095	0.034	n.a.	
Aminophylline	-0.103	0.045	-0.078	0.087	-0.096	0.017
Methylprednisolone	-0.170	0.001	-0.091	0.046	-0.051	0.206

B – beta coefficient; *p* – probability; n.a. – not applicable (a variable excluded from the model); ACE – angiotensin converting enzyme.

Table 6

Variables significantly associated with a total score of EQ-5D in the models of multivariable linear regression

Variables	7th day		30th day		90th day	
	B	*p*	B	*p*	B	*p*
MV	0.019	0.703	-0.026	0.549	-0.038	0.324
Age	-0.002	0.157	-0.003	0.018	-0.003	0.049
Previous surgery	0.010	0.848	-0.020	0.674	n.a.	n.a.
Cardiomyopathy	n.a.	n.a.	n.a.	n.a.	-0.044	0.298
Cerebrovascular disease	n.a.	n.a.	-0.024	0.717	-0.030	0.606
Chronic kidney disease	-0.088	0.175	-0.129	0.044	-0.053	0.310
Hypertension	-0.018	0.760	0.012	0.828	n.a.	n.a.
Diabetes mellitus type 1	-0.153	0.032	n.a.	n.a.	n.a.	n.a.
Amlodipine	-0.140	0.016	-0.030	0.563	-0.041	0.368
ACE inhibitors	-0.049	0.431	n.a.	n.a.	n.a.	n.a.
Aminophylline	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Methylprednisolone	-0.0157	0.003	n.a.	n.a.	n.a.	n.a.

B – beta coefficient; *p* – probability; n.a. – not applicable (a variable excluded from the model); MV – mechanical ventilation; ACE – angiotensin converting enzyme.

Discussion

The results of this study showed that people with community-acquired pneumonia who had been treated in hospital suffered for weeks after recovery from poor quality of life, due to the acute disease, particularly if they were managed with mechanical ventilation and within an intensive care unit setting. Other researchers have also reported similar findings but, as a rule, with mixed intensive-care patient population, suffering from a variety of diseases that caused acute lung injury and/or respiratory distress syndrome [15, 21, 22]. Only recently, the researchers focused exclusively on the quality of life measurement in patients with pneumonia because such studies had been rare in the past [12].

Other studies are different from our research in some important methodological points. For example, one study included only subjects suffering from severe influenza pneumonia and another one investigated patients with serious lower respiratory tract infections, particularly interested in pneumococcal pneumonia [23, 24]. They assessed the quality of life with the same rating instrument as we did, but only cross-sectionally, omitting the prospective data collection during the longer period. In addition, these and other similar studies, having been conducted so far, did not pay particular attention either to the effects of mechanical ventilation or to the subjects treated within intensive care unit settings as it was the case in our study. The magnitude and the pattern of the change of the quality of life in our study, both within and between subgroups, could be considered clinically important based on the comparisons with the existing data in the field [12, 19, 21–24].

The existing knowledge suggest that pro-inflammatory response, and, to some extent, brain dysfunction are probably the main factors deteriorating the quality of life of the mechanically ventilated CAP patients [17]. It is well known that the activation of immunological cells and the release of inflammatory mediators during pneumonia contributed to both the elimination of the invaders and the injury of the patient, depending on the balance of favorable and harmful factors [25]. Researchers found that in the mechanically ventilated patients with pneumonia there was an large increase of serum and local cytokines like interleukin 6 (IL-6), IL-8 and IL-10 [13, 14]. In addition, the patients with severe

CAP could develop brain dysfunction, and in some of them investigators revealed a significant deterioration of cerebral blood vessels [26, 27]. Cytokine effects, synaptic dysfunction of brain neurotransmitters (particularly dopaminergic, serotonergic, glutamatergic and opioid synapses), disruption of circadian rhythm and the disturbances of neurotrophic mediators (e.g., brain derived neurotrophic factor) are proposed biological mechanisms contributing to fatigue, pain, emotional and social functioning which constitute domains of quality of life perception [17].

There were several demographic and clinical factors, such as age, the presence of chronic kidney disease and diabetes mellitus type 1 that were slightly, but independently associated with the unfavorable outcome in our research. Some researchers identified the pattern of radiological pulmonary findings, prolonged hospital stay, older age, poor functioning at the baseline and persistent weakness during ICU treatments as the risk factors for poor quality of life after surviving pneumonia and/or other severe pulmonary disease requiring mechanical ventilation [22, 28]. Obviously, the existing knowledge about the putative, independent risks is limited and further studies investigating the issue are required.

In our study, univariate analysis revealed many additional factors which were associated with poor quality of life, either in the experimental or the control group, regarding marital status, previous surgery, cardiomyopathy, cerebrovascular disease, diabetes mellitus type 1, hypertension and pulmonary emphysema as well as near a dozen of drugs. However, it is very likely that these factors represent rather the cofounders than the independent predictors of lower scores of the quality of life measurements in our study populations. Indeed, it is well documented that prevalent chronic diseases caused enduring, negative impact on the patient's quality of life resulting in significant medical and socio-economic burden of the modern societies, particularly respiratory, cardiovascular, musculoskeletal, cerebrovascular and mental illnesses [29-34]. These comorbidities are also linked with the use of drugs that were identified in our study as putative risks like amlodipine and methylprednisolone. Researchers had already proved that the use of both, calcium channel blockers and corticosteroids in the treatment of chronic disease, in fact, increased patients' quality of life [35-37]. Therefore, it seems that the quality of life in the mechanically ventilated CAP patients is influenced rather by the complex milieu of numerous subtle-acting, highly interconnected, intrinsic and acquired factors than by the profound effects of leading causes.

Results of EQ5D-5L questionnaire showed that the use of MV as a part of CAP treatment in our study was associated with poorer outcome in terms of mobility, self-care and usual activities as well as to lesser extent, pain/discomfort and anxiety/depression domains. The others just reported that the patients with CAP had the decrease of both the total EQ-5D weighted index and the total VAS score, indicating poor quality of life in general sense; but, mobility, self-care and usual activities were much affected, similarly to our observations [21]. In intensive-care patients with pneumonia and/or sepsis the high Simplified Acute Physiology Score (SAPS) II predicted low scores on EQ-5D dimensions, particularly of physical components that were in good agreement with our results [15]. In our study, the negative trend for the first three domains was maintained during 7, 30 and 90 days after the hospitalization, and for the last other two only on days 7 and 90. In general, similar findings were observed in a previous study which showed that the use of MV was linked with the poorer quality of life, far beyond the end of active treatment, at 3 and 12 months after discharge from ICU [28]. There were suggestions that the presence of symptoms of CAP beyond 28 days and any impairment in quality of life was a reflection of age and comorbidity rather than persistent effects of pneumonia itself [38]. However, the effects of other risk factors that were not followed in this study, but acting independently on the quality of life could not be excluded yet.

The main limitations of our study are moderate-sample size, the use of a single quality of life instrument, reliance primarily on variables used in routine health-care and the possibility of existence of unidentified significant, independent risks as well as selection bias. We powered our study to detect the difference of weighted EQ-5D-5L index of presumed clinical significance between the study arms at prespecified level only in the survivors after the treatment as the intubation for MV precluded baseline measurements. The details about biological basis of the outcomes observed in our research remained poorly understood and this requires further prospective research studies, probably with combination of experimental and clinical approaches. For example, novel biomarkers, pro-adrenomedullin and pro-atrial natriuretic peptide have been recently found superior to conventional laboratory parameters like leukocyte numbers, C-reactive protein and procalcitonin in prediction of poor quality of life of patients with CAP [21].

Our study included only the survivors who could provide us with reliable data at weeks after the hospital treatment. Consequently, selection bias, and, to some extent, bias due to the missing data about newly emerged comorbidities and their treatments could not be completely excluded. However, selection bias is often avoidable in published studies that investigate the quality of life, as is shown in the studies in orthopedics, neurology, vascular surgery and treatment of obesity and osteoporosis, which also used EQ-5D as the primary instrument of quality of life assessment [39–42].

Conclusion

Patients with MV tend to have poorer quality of life especially in three domains presented in the study. The main reasons are the presence of chronic comorbidities in this population which require MV, especially chronic kidney disease and diabetes mellitus type 1 which was of the greatest significance. The influence of individual factors is relatively mild, requiring a holistic approach to quality of life. The determinants of poor quality of life in this population have extended the period of active treatment that requires permanent care, especially bearing in mind the effects of age.

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