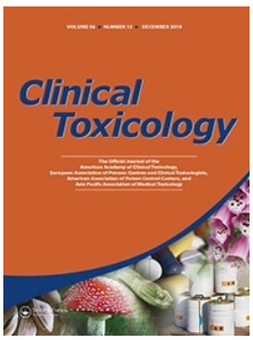

Clinical Toxicology

ISSN: 1556-3650 (Print) 1556-9519 (Online) Journal homepage: https://www.tandfonline.com/loi/ictx20

Health-related quality of life determinants in survivors of a mass methanol poisoning outbreak: six-year prospective cohort study

Jan Rulisek, Petr Waldauf, Jan Belohlavek, Martin Balik, Katerina Kotikova, Jiri Hlusicka, Manuela Vaneckova, Zdenek Seidl, Pavel Diblik, Jan Bydzovsky, Jarmila Heissigerova, Pavel Urban, Michal Miovsky, Jaroslav Sejvl, Daniela Pelclova & Sergey Zakharov

To cite this article: Jan Rulisek, Petr Waldauf, Jan Belohlavek, Martin Balik, Katerina Kotikova, Jiri Hlusicka, Manuela Vaneckova, Zdenek Seidl, Pavel Diblik, Jan Bydzovsky, Jarmila Heissigerova, Pavel Urban, Michal Miovsky, Jaroslav Sejvl, Daniela Pelclova & Sergey Zakharov (2020): Health-related quality of life determinants in survivors of a mass methanol poisoning outbreak: six-year prospective cohort study , Clinical Toxicology, DOI: 10.1080/15563650.2019.1702994

To link to this article: https://doi.org/10.1080/15563650.2019.1702994

CLINICAL TOXICOLOGY
https://doi.org/10.1080/15563650.2019.1702994

Taylor & Francis
Taylor & Francis Group

CLINICAL RESEARCH

Health-related quality of life determinants in survivors of a mass methanol poisoning outbreak: six-year prospective cohort study

Jan Rulisek[a], Petr Waldauf[b], Jan Belohlavek[c], Martin Balik[a], Katerina Kotikova[d,e], Jiri Hlusicka[d,e], Manuela Vaneckova[f], Zdenek Seidl[f], Pavel Diblik[g], Jan Bydzovsky[g], Jarmila Heissigerova[g], Pavel Urban[d,e], Michal Miovsky[h], Jaroslav Sejvl[h], Daniela Pelclova[d,e] and Sergey Zakharov[d,e]

[a]Department of Anesthesia and Intensive Care, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic; [b]Department of Anesthesia and Intensive Care, Third Faculty of Medicine, Charles University and Royal Vinohrady Teaching Hospital, Prague, Czech Republic; [c]Department of Cardiology and Angiology, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic; [d]Department of Occupational Medicine, First Faculty of Medicine, Charles University, Prague, Czech Republic; [e]Toxicological Information Centre, General University Hospital, Prague, Czech Republic; [f]Department of Radiology, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic; [g]Department of Ophthalmology, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic; [h]Department of Addictology, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic

ABSTRACT

Purpose: The effect of acute methanol poisoning on the follow-up quality of life of survivors in mass poisoning outbreaks is not known. The objective of this is to study the impact of visual and central nervous system (CNS) sequelae of methanol poisoning on long-term health-related quality of life (QoL) of survivors, its clinical determinants, and dynamics.

Materials and methods: A total of 54 patients with confirmed methanol poisoning (mean age 46.7 ± 13.4 years, 9 females) were examined consequently three times within six-year prospective cohort study and compared to 23 controls with the history of chronic alcohol abuse. The following tests were performed: SF-36 QoL questionnaire, visual evoked potentials (VEP) of optic nerve, ocular examination with retinal nerve fiber layer (RNFL) thickness measurement, brain magnetic resonance imaging (MRI), and biochemical and toxicological tests.

Results: Acute methanol poisoning led to significant decrease in physical component summary (PCS) compared to PCS of age-adjusted controls (mean score with SD 46.8 ± 11.0 versus 52.3 ± 9.4 points; $p = .003$). In 17/40 (42.5%) patients with three rounds of examination, signs of severe disability (≤30 points in at least one score) were present six years after discharge, with negative dynamics of PCS score during the observation period. The patients with abnormal RNFL thickness had lower PCS (mean difference 10.5 points; 95%CI 3.5–17.5, $p = .004$) and mental component summary score (9.5 points; 95%CI 1.9–17.1, $p = .015$) compared to the patients with normal RNFL. Signs of physical and mental adaptation to long-term visual sequelae were registered with gradual reduction of difference in most of physical and mental components scores compared to the patients with normal RNFL during six years of observation. Signs of hemorrhagic brain lesions were associated with permanent decrease of PCS score (mean difference 7.4 points; 95%CI 0.6–14.0; $p = .033$), bodily pain (8.7 points; 95%CI 1.6–17.6; $p = .018$), and social functioning (8.2 points; 95%CI 3.0–17.4; $p = .005$) six years after discharge. No effect of type of antidote (fomepizole versus ethanol) and extracorporeal enhanced elimination modality (intermittent hemodialysis versus continuous renal replacement therapy) applied in hospital on long-term QoL was found (all $p > .05$).

Conclusion: Acute methanol poisoning was associated with a significant decrease of health-related quality of life of survivors persisting for at least six years after discharge. The more pronounced decrease in QoL scores was observed in the patients with hemorrhagic brain lesions and visual sequelae of poisoning with abnormal RNFL thickness.

ARTICLE HISTORY
Received 13 September 2019
Revised 12 November 2019
Accepted 3 December 2019

KEYWORDS
Methanol poisoning; quality of life; visual sequelae; CNS sequelae; brain damage

1. Introduction

1.1. Background

Methanol is a severely toxic alcohol that is used as an antifreeze, solvent, coolant, fuel, or as a primary agent in the production of other chemicals and mixtures [1–2]. Mass or cluster poisonings typically occur due to illicit alcohol consumption that contains high methanol concentrations [3–5]. A large number of fatalities and severe health sequelae in survivors present a serious problem for national health systems throughout the world, mainly in developing countries [6–9].

The cornerstones in methanol poisoning treatment are timely application of antidote, ethanol or fomepizole,

CONTACT Jan Rulisek jan.rulisek@vfn.cz Department of Anesthesia and Intensive Care, First Faculty of Medicine, Charles University and General University Hospital, U Nemocnice 2, 120 00 Prague 2, Czech Republic

extracorporeal elimination techniques (intermittent hemodialysis [IHD] or continuous renal replacement therapy [CRRT]), alkalinization with bicarbonate, folate supplementation, and complex intensive care measures [10–12]. If therapeutic measures are inadequate or delayed, visual impairment due to toxic effects of formic acid on the retinal ganglion cells and axons of the optic nerve can lead to visual loss up to complete blindness in the most severe cases [13–16].

Bilateral hemorrhagic necrosis of the basal ganglia, namely the putamen and in the subcortical white matter, are typical magnetic resonance imaging (MRI) findings in up to 50% of survivors of acute methanol poisoning [17]. Brain lesions are often associated with extrapyramidal syndrome, which is characterized by rigidity, dystonia, bradykinesia, mild tremor, and cognitive deficits [18–20].

1.2. Importance

Several prognostic factors have been identified for hospital outcome in acute methanol poisoning. The severity of metabolic acidosis, blood ethanol concentration, coma at admission, and time to treatment after methanol exposure are among them [21–23]. However, there is increasing community interest in the long-term functional recovery and health-related quality of life of poisoning survivors, as well as the factors that contribute to recovery after acute methanol poisoning [24–27]. Long-term health sequelae of poisoning may be responsible for decreased mobility, difficulty walking, chronic pain, problems in social life, and reduced chances to regain the same working position due to decreased visual acuity or neurological symptoms [28,29].

At present, no studies have investigated the impact of long-term visual and central nervous system (CNS) sequelae on health-related quality of life of survivors during the years following discharge from the hospital. How to account for the influence of brain lesions, optic nerve, and retinal damage on the physical and mental condition of these patients, as well as their need for rehabilitation, social re-adaptation, and psychological support, remains unclear. There is no data available in the literature as to whether different treatment modalities (application of ethanol versus fomepizole, intermittent versus continuous methods of renal replacement therapy) during hospitalization may have an independent impact on the long-term quality of life in methanol-poisoned patients. These facts make evaluation of the effectiveness of therapeutic interventions, prognosis, and timely indication of medical and psychological measures to enhance the quality of life of methanol-poisoning survivors challenging.

There are several quality of life scoring systems that can be applied in the longitudinal studies. The Short Form 36 (SF-36) is a 36-item, patient-reported survey of his or her health state; it measures health-related quality of life via two components: physical and mental. The original SF-36 came from the Medical Outcome Study (MOS) performed by the RAND Corporation [30]. Since then, a group of researchers from the original study released a commercial version of the SF-36, while the original SF-36 is available license free from RAND in the public domain. The SF-36 comprises eight scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0–100 scale on the assumption that each question carries equal weight. Lower scores indicate more disability, while higher scores suggest less disability. Scores greater than 50 points indicate mild disability, while scores under 30 points indicate severe overall disability. The physical component summary (PCS) considers physical functioning (PF), role physical (RF), bodily pain (BP), and general health (GH) perception. The mental component summary (MCS) considers vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). The PCS comprises 22 questions, and the MCS contains 14 questions, all of which are strict and easy to understand.

1.3. Goals of this investigation

We present the data based on a methanol mass poisoning outbreak with more than 130 cases of poisoning and more than 50 deaths [31,32]. Here, we report the findings of a prospective cohort study that investigated the impact of the character of long-term health sequelae of acute methanol poisoning, clinical determinants of the poisoning severity, and different treatment modalities, on the quality of life of survivors during 6 years post-discharge from the hospital. We analyzed associations of the quality of life with admission laboratory data (arterial blood pH, serum methanol concentration), treatment modalities, and results of objective examinations performed during the follow-up.

For evaluation of the association of quality of life with long-term visual sequelae of poisoning, we applied the results of visual evoked potential (VEP) measurements and optical coherence tomography (OCT) with retinal nerve fibers layer thickness (RNFL) measurements. The association of quality of life with CNS sequelae of poisoning was examined based on the results of brain MRI. To exclude the possible impact of chronic alcohol abuse on the quality of life of survivors of poisoning, we recruited the control group with a history of chronic alcohol abuse registered in the addictology department of the hospital.

During the 6 years after the mass methanol poisoning outbreak in 2012, we performed three consecutive clinical examinations of the survivors according to the same standardized clinical protocol, which included the SF-36 questionnaire, in the same medical facility to determine the dynamics of changes of health-related quality of life of these patients and its association with key clinical and laboratory determinants.

2. Materials and methods

2.1. Study design and setting

This prospective, observational cohort study included the patients with confirmed methanol poisoning treated during a poisoning outbreak [5,31,32]. The clinical, toxicological, and biochemical data were collected by applying a standardized data collection form. Information on the treatment and

outcome was obtained from hospital discharge reports. The follow-up clinical examinations were performed three times in the same hospital: 2, 4, and 6 years after discharge. The study was approved by institutional Ethics Committee.

2.2. Patient population

All cases of hospital admission with confirmed methanol poisoning were mandatorily reported to the Ministry of Health and Toxicological information center, and nationwide daily monitoring of the situation in all hospitals was established. All patients hospitalized with confirmed methanol poisoning were eligible for this study.

For controls, healthy subjects of the same ethnicity with the history of chronic alcohol abuse – who were visiting the addictology department for outpatient treatment of alcoholism—were recruited. Exclusion criteria for the controls were any ocular and CNS pathology that prevents visual function (VEP) examination and estimation of physical and mental components of SF-36. The control group was not regulated with regards to age, gender, chronic somatic co-morbidities (diabetes mellitus, arterial hypertension, and others), peripheral nervous system diseases, and further visual pathology (for example, refractive error) if VEP examination was possible. Patients with methanol poisoning were treated in accordance with the American Academy of Clinical Toxicology and European Association of Poisons Centers and Clinical Toxicologists practice guidelines for the treatment of methanol poisoning and with current recommendations [10,33–35].

The protocol for clinical examinations included ocular examination with standard ophthalmologic tests, cerebral computed tomography (CT) or MRI, and neurological examination. Patients were considered to have visual sequelae of methanol poisoning if the symptoms of optic neuropathy were documented during hospitalization, with pathologic findings on visual acuity, perimeter, color vision, contrast sensitivity, and persisting lesions on fundoscopy on discharge from the hospital. Furthermore, patients were considered to have CNS sequelae of poisoning if symmetrical necrosis and hemorrhages of basal ganglia and subcortical white matter compatible with the diagnosis of acute methanol poisoning were present on brain CT or MRI [36].

2.3. Follow-up investigation protocol

The follow-up clinical examination protocol that was applied three times during the 6-year observation period included complete ocular examination and standard ophthalmic tests, OCT with RNFL, VEP, MRI of the brain, addictological, neurological, and neuropsychological examinations, biochemical tests (electrolytes, glucose, glycohemoglobin, albumin, prealbumin, renal and hepatic tests, cholesterol, lipids, thyroid-stimulating hormone, vitamin B_{12}, carbohydrate deficient transferrin, complete blood count, and hematocrit), ethyl glucuronide in urine, and standardized SF-36 Health Survey questionnaire forms. The examiners were masked to the admission laboratory parameters, severity of poisoning, clinical course, treatment measures, and outcomes in methanol-poisoned patients on discharge from hospitals, as well as to each other's results.

2.4. Calculations and data analysis

Statistical analysis was performed in Stata 15.1 (StataCorp LLC, Texas, USA). Basic descriptive statistics were calculated for all variables, which were subsequently tested for normality using the Kolmogorov–Smirnov test. The chi-square test was used to compare frequency counts of demographic and clinical categorical variables. The bivariate relationship was assessed using Pearson's correlation coefficient. A linear mixed effects model was applied to study the longitudinal relationship between demographic, clinical, and laboratory parameters, and the results of SF-36 calculations during the study period. The dependent variables in this model were the scores of the quality of life from the SF-36 questionnaire.

The independent variables included in the model were: age, sex, severity of metabolic acidosis (arterial blood pH), acute serum concentration of methanol, results of P1 latency and N1P1 amplitude measurements of VEP, results of RNFL measurements by OCT, and findings from brain MRI. The models were adjusted for age and sex. Two-sided statistical significance was set at $p < .05$.

3. Results

3.1. Patients and baseline characteristics

During the Czech methanol mass poisoning outbreak, 108 patients were treated in hospitals with acute methanol poisoning. Of these 108 patients (mean age with SD 50.9 ± 2.6 years), 24 patients with a mean age of 54.4 ± 5.9 years died from acute methanol poisoning during hospitalization. Altogether, 84 patients with a mean age of 49.9 ± 3.0 years, including 27 patients with MRI signs of toxic brain damage, survived and were discharged. Of those who survived poisoning, 54 patients (64%) agreed to participate and were included in the prospective study of long-term health sequelae of poisoning and health-related quality of life.

Of 54 patients included in the study, 8 patients filled out only one quality of life questionnaire and 6 patients completed two questionnaires during the study period (10 patients died during the follow-up period and 4 patients participated in less than three rounds of examination), while 40 patients completed the questionnaire during all three rounds of examinations during the 6-year observation. The control group of 23 recruited patients (patients being examined during a randomly chosen study period) with a history of chronic alcohol abuse—consisting of 12 females and 11 males with mean age 53.5 ± 7.9 years—completed the quality of life questionnaire during the first round of clinical examinations. They also underwent an ophthalmology examination (VEP, OCT with RNFL, perimeter, and color vision) and electromyography. Basic demographic, clinical, and laboratory data of the patients from the study population and the controls are presented in Table 1.

Table 1. Basic demographic, clinical, and laboratory data of the patients from the study population ($n = 54$) and control group ($n = 23$), means with SD and absolute numbers (%).

Variable	Methanol-exposed group	Control group	OR	p
Age, years	46.7 [43.1; 50.4; 95%CI]	53.4 [49.9; 51.0; 95%CI]	–	.009
Gender (M/F)	45/9	11/12	–	.001
Chronic alcoholism	38 (70%)	23 (100%)	–	–
Hypertension	22 (40.7%)	4 (17.4%)	3.7 [1.1;12.6]	.047
Diabetes mellitus	8 (14.8%)	1 (4.3%)	4.2 [0.5;35.7]	.191
Ischemic heart disease	8 (14.8%)	1 (4.3%)	4.2 [0.5;35.7]	.191
Hepatopathy	35 (64.8%)	3 (13.0%)	15.6 [4.0;60.6]	<.001
Abnormal visual perimeter	24 (44.4%)	3 (13.0%)	6.2 [1.6;23.4]	.008
Abnormal color vision	25 (46.3%)	3 (13.0%)	6.6 [1.8;25.3]	.005
Refractive error	18 (33.3%)	16 (69.6%)	4.1 [1.4;11.7]	.003
Abnormal RNFL	12 (22.2.0%)	2 (8.7%)	8.9 [1.9;42.3]	.159
Abnormal VEP	25 (46.3%)	5 (21.7%)	3.6 [1.2;11.2]	.043
Peripheral polyneuropathy	20 (37.0%)	1 (4.3%)	11.1 [1.5;44.7]	.003
Methanol-induced brain damage	23 (42.6%)	–		
Methanol-induced brain hemorrhages	18 (33.3%)	–		
MetOH*, mg/L	1290.0 ± 390.0	–		
Arterial blood pH*	7.21 ± 0.06	–		
Median time to treatment, hours	30 [IQR 14–40]	–		
Antidote (ethanol/fomepizole/no)	40/11/3	–		
Dialysis (IHD/CRRT/no)	24/17/13	–		

M: male; F: female; MetOH: serum methanol concentration; IHD: intermittent hemodialysis; CRRT: continuous renal replacement therapy; RNFL: retinal nerve fibers layer thickness on optical coherence tomography; VEP: visual evoked potentials.
*: at admission to hospital with acute methanol poisoning.

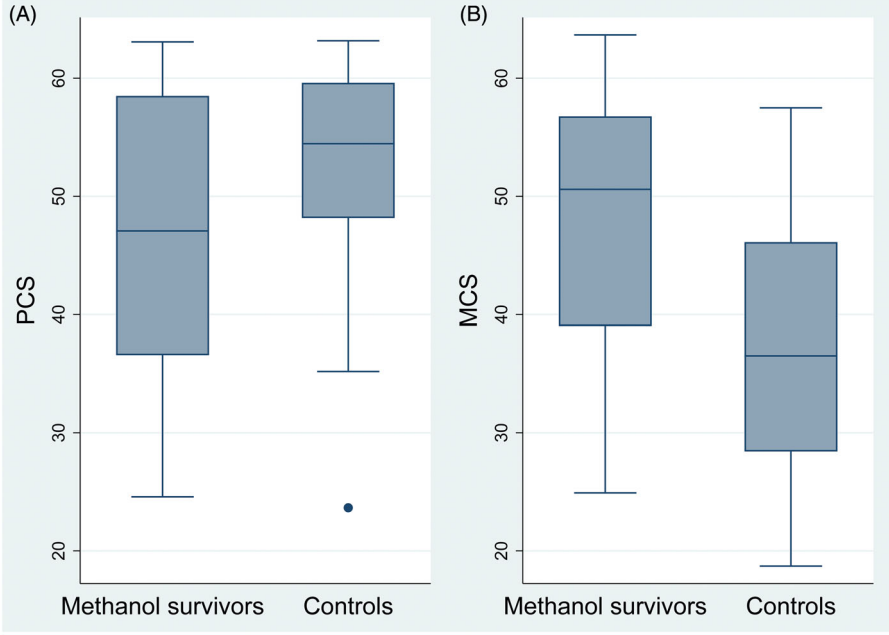

Figure 1. (A) Physical component summary score in survivors of acute methanol poisoning versus controls. (B) Mental component summary score in survivors of acute methanol poisoning versus controls.

3.2. Six-year dynamics of physical and mental components summaries of quality of life

The acute methanol poisoning survivors demonstrated a significantly lower mean PCS score compared to the controls (Figure 1(A)), but a higher MCS score (Figure 1(B)). The age of the patients significantly influenced PCS, PF NBS, BP NBS, and RE NBS. On the other hand, gender had no effect on any component of the scores (all $p > .05$). After adjustment for age, the difference in PCS score became even greater between the groups, while the effect of age was less significant for MCS (Table 2).

The mean scored for all SF-36 components in the study population were lower than the limit of at least 50 points, data that indicate mild overall disability. However, no component in the study population demonstrated a mean score under 30 points that is indicative of severe overall disability (Table 3). Nevertheless, the absolute number of survivors with the score $\leq$ 30 points in at least one SF-36 component after 6 years of observation was high: 17/40 (42.5%). These patients had brain necrotic lesions with signs of hemorrhages on MRI in 8/17 (47%) cases.

The dynamics of changes in separate PCS and MCS components in the three rounds of examinations during the 6-year observation was insignificant (Table 3). Only the overall feeling of bodily pain significantly worsened with time. There was a notable decline in the dynamics of the PCS score

Table 2. Physical and mental component summaries in the survivors of methanol poisoning versus controls (unadjusted and adjusted for age and gender).

Shortcut	Parameter	Groups		Two sample *t*-test		Delta	Linear regression (age adjusted)	
		Methanol	Controls	Delta	*p*	(age adjusted)	*p* (groups)	Coeff. (age) (*p*)
PCS	Physical component summary	46.8	52.3	−5.5	**.039**	−8.2	**.003**	**−0.4 (<.001)**
MCS	Mental component summary	47.3	37.2	10.1	**.002**	−10.4	**.005**	NS
PF NBS	Physical functioning	46.8	51.2	−4.4	.056	−8	**.001**	**−0.52 (<.001)**
RP NBS	Role limitations due to physical health	46.2	45.6	0.6	.834	−0.75	.83	NS
BP NBS	Bodily pain	49.3	50.8	−1.5	.62	−3.2	.35	**−0.3 (<.02)**
GH NBS	General health	43.5	45.3	−1.8	.47	3.4	.47	NS
VT NBS	Vitality	48.8	48.2	0.6	.83	−0.63	.82	NS
SF NBS	Social functioning	45.3	36.9	8.4	**.016**	−7.19	.016	NS
RE NBS	Role emotional	45.7	38.1	7.6	**.023**	5.5	.154	**−0.26 (.042)**
MH NBS	Mental health	47.7	41.5	6.2	**.039**	−10.08	**.002**	NS

$p < .05$ was considered significant (bold figures).
NS: not significant.

Table 3. Dynamics of changes of separate components of PCS and MCS in survivors of acute methanol poisoning during six years of observation (means with SD).

Shortcut	Parameter	1st exam	2nd exam	3rd exam	Delta 1st/3rd	*p* (linear mixed effect model)
PF NBS	Physical functioning	47.2 ± 11.0	45.7 ± 10.3	46.7 ± 11.8	−0.5	.3
RP NBS	Role limitations due to physical health	46.2 ± 11.0	46.4 ± 12.4	46.9 ± 10.3	0.7	.91
BP NBS	**Bodily pain**	**49.8 ± 13.6**	**47.7 ± 13.7**	**46.9 ± 12.9**	**−2.9**	**.037**
GH NBS	General health	43.7 ± 12.8	44.8 ± 12.4	44.7 ± 12.6	1.0	.45
VT NBS	Vitality	49.2 ± 11.3	51.6 ± 11.7	50.1 ± 10.5	0.9	.12
SF NBS	Social functioning	45.9 ± 12.2	46.4 ± 11.4	46.6 ± 11.2	0.7	.76
RE NBS	Role emotional	46.0 ± 12.6	44.6 ± 12.9	46.6 ± 12.6	0.6	.41
MH NBS	Mental health	48.5 ± 11.3	49.1 ± 11.1	49.4 ± 10.0	0.9	.47

$p < .05$ was considered significant (bold figures).

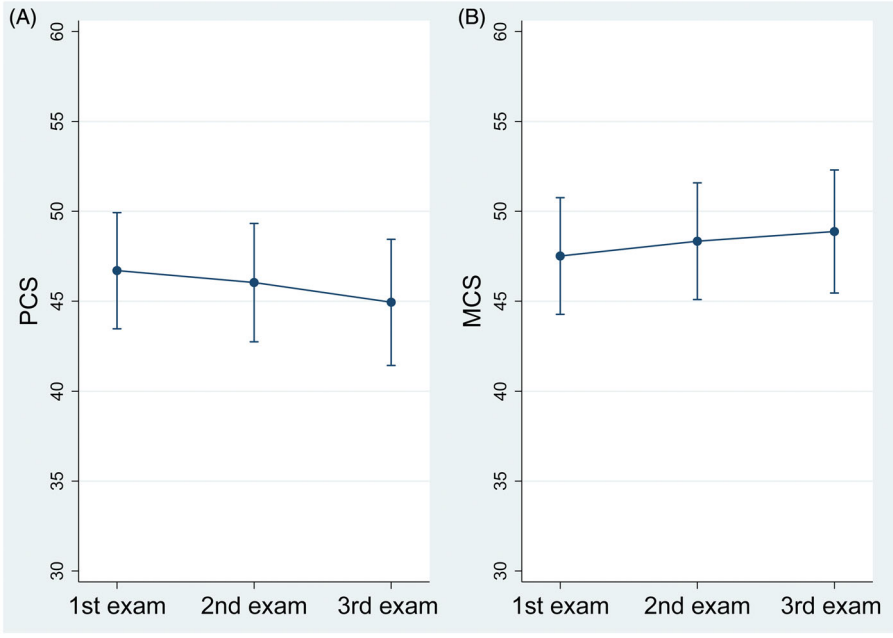

Figure 2. (A) Dynamics of physical component summary score changes in survivors of acute methanol poisoning during six years of observation. (B) Dynamics of mental component summary score changes in survivors of acute methanol poisoning during six years of observation.

during the study period (Figure 2(A)). On the other hand, MCS demonstrated a slow increase during the follow-up (Figure 2(B)).

3.3. Admission laboratory data, poisoning treatment modalities, and the quality of life of survivors of methanol poisoning

The effect of admission arterial blood pH as the indicator of the severity of acute methanol poisoning on the follow-up quality of life of survivors was not significant (Figure 3(A,B)). There was a borderline relationship between higher arterial blood pH and higher PCS (mean slope 13.8 ± 7.5; 95% confidence interval [CI] − 0.9 to 28.6; $p = .066$) and MCS (mean slope 9.4 ± 7.2; 95%CI −4.7 to 23.5; $p = .190$). Serum methanol concentration had an insignificant effect on PCS (mean slope −2.7 ± 1.4; 95%CI −5.5 to 0.1; $p = .060$) and MCS (mean slope 1.7 ± 1.4; 95%CI −4.4 to 1.0; $p = .209$) after adjustment for age.

The patients had been treated in hospitals with antidotes to block alcohol dehydrogenase: ethanol in 74% of cases,

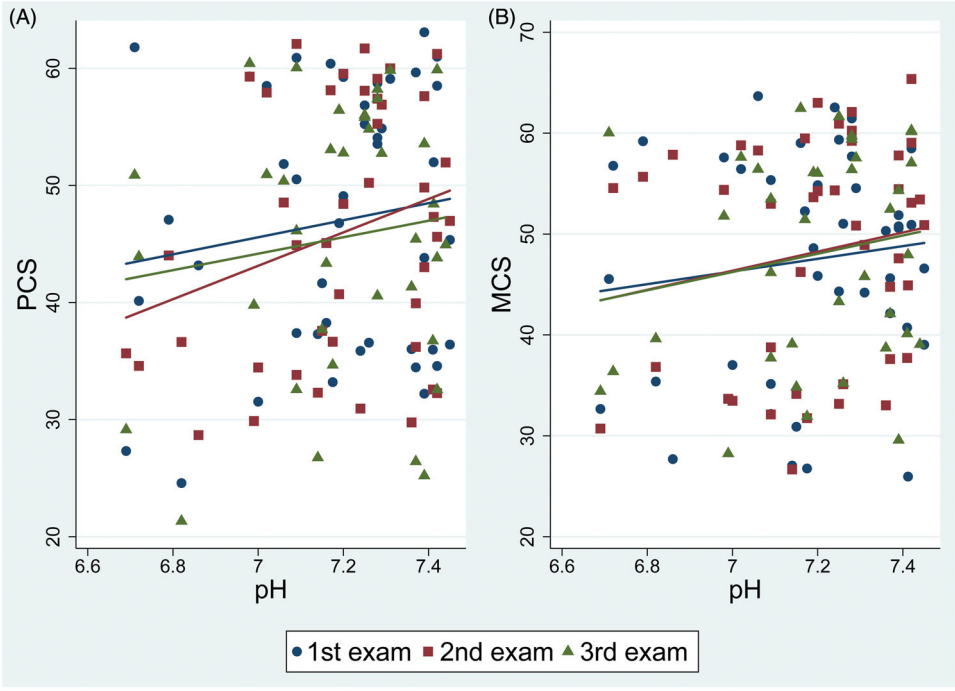

Figure 3. (A) Arterial blood pH at admission and physical component summary score of survivors of acute methanol poisoning. (B) Arterial blood pH at admission and mental component summary score of survivors of acute methanol poisoning.

Table 4. Association of latency P1 and amplitude N1P1 of visual evoked potentials with the follow-up quality of life of survivors of acute methanol poisoning.

		Linear mixed effect model, slope, 95%CI, *p*			
Shortcut	Parameter	OD P1	OS P1	OD N1P1	OS N1P1
PCS	Physical component summary	**−0.7 (−1.2; −0.2), *p* = .004**	**−0.4 (−0.7; −0.1), *p* = .007**	**1.0 (0.08; 1.9), *p* = .024**	**1.0 (0.03; 2.0), *p* = .042**
MCS	Mental component summary	**−0.7 (−1.2; −0.2), *p* = .005**	−0.1 (−0.4; 0.2), *p* = .4	0.3 (−0.7; 1.2), *p* = .55	0.3 (−0.6; 1.3), *p* = .49
PF NBS	Physical functioning	**−0.8 (−1.1; −0.4), *p*<.001**	**−0.4 (−0.6; −0.1), *p* = .003**	**0.9 (0.2; 1.7), *p* = .01**	**1.0 (0.2; 1.8), *p* = .013**
RP NBS	Role limitations due to physical health	**−0.7 (−1.1; −0.2), *p* = .006**	**−0.4 (−0.7; −0.1), *p* = .012**	0.9 (−0.05; 1.8), *p* = .063	0.8 (−0.2; 1.8), *p* = .105
BP NBS	Bodily pain	**−0.8 (−1.4; −0.2), *p* = .009**	**−0.5 (−0.8; −0.08), *p* = .018**	**1.2 (0.08; 2.3), *p* = .036**	**1.2 (0.02; 2.5), *p* = .046**
GH NBS	General health	**−0.7 (−1.3; −0.2), *p* = .009**	−0.2 (−0.5; 0.1), *p* = .26	0.9 (−0.1; 1.9), *p* = .087	0.9 (−0.1; 1.9), *p* = .197
VT NBS	Vitality	**−0.8 (−1.2; −0.3), *p* = .002**	−0.2 (−0.5; 0.2), *p* = .33	0.7 (−0.3; 1.6), *p* = .162	0.5 (−0.5; 1.5), *p* = .308
SF NBS	Social functioning	**−0.7 (−1.1; −0.3), *p* = .002**	**−0.3 (−0.6; −0.1), *p* = .044**	0.4 (−0.4; 1.3), *p* = .32	0.5 (−0.4; 1.5), *p* = .27
RE NBS	Role emotional	**−0.8 (−1.3; −0.3), *p* = .001**	**−0.3 (−0.6; −0.01), *p* = .046**	0.7 (−0.2; 1.7), *p* = .145	0.7 (−0.3; 1.7), *p* = .190
MH NBS	Mental health	**−0.7 (−1.2; −0.3), *p* = .002**	−0.1 (−0.5; 0.2), *p* = .37	0.5 (−0.5; 1.5), *p* = .35	0.5 (−0.5; 1.5), *p* = .36

OD: oculus dexter; OS: oculus sinister; P1: latency P1 of visual evoked potentials; N1P1: amplitude N1P1 of visual evoked potentials.
$p < .05$ was considered significant (bold figures).

fomepizole in 20% of cases, and without antidote in 6% of cases. There was no effect of type of antidote applied in the hospital (fomepizole versus ethanol) on the follow-up quality of life of the patients. For PCS, the mean difference was −3.1 (95%CI −10.0 to 3.7; $p = .367$), while for MCS, the mean difference was 0.2 (95%CI −6.2 to 6.6; $p = .947$). The association of separate components of physical and mental scores with the type of antidote was also insignificant (all $p > .05$).

In 76% of patients in the study population, extracorporeal-enhancing elimination was applied. IHD was utilized in 44% of cases, and the methods of CRRT modalities were used in 32% of cases. There was no effect from type of enhanced elimination method applied in the hospital (IHD versus CRRT) on the follow-up quality of life of the patients. For PCS, the mean difference was −5.7 (95%CI −14.0 to 2.6; $p = .181$), while for MCS, the mean difference was 4.0 (95%CI −4.6 to 12.6; $p = .363$). The association of separate components of physical and mental scores with the modality of extracorporeal enhancing elimination was also insignificant (all $p > .05$).

3.4. Effect of long-term visual sequelae on the quality of life of survivors of methanol poisoning

The association between optic nerve function measured by VEP and quality of life is presented in Table 4. The prolonged P1 latency reflected the grade of demyelination of axons of the optic nerve and was negatively associated with both PCS and MCS scores: The longer the latency, the lower the PCS, MCS, and their separate components. The association was stronger for right eyes (oculus dexter [OD]) compared to for left eyes (oculus sinister [OS]) because the standard deviation in OD measurements was lower. However, the difference in mean P1 latency between two eyes was not significant (115.3 ± 7.1 sec for OD versus for 117.4 ± 10.7 sec for OS; $p = .240$).

The association between the N1P1 amplitude of evoked potentials of the optic nerve and the components of both physical and mental scores was less strong (Table 4). A decrease in the amplitude reflects acute degeneration of optic nerve axons, the most severe damage of the visual

Table 5. Effect of long-term visual sequelae of poisoning (normal RNFL findings versus abnormal RNFL findings) on the follow-up quality of life of survivors of acute methanol poisoning.

		The unpaired *t*-test, mean difference in the score of the patients with normal RNFL versus abnormal RNFL, 95%CI, *p*		
Shortcut	Parameter	1st exam	2nd exam	3rd exam
PCS	Physical component summary	**10.5 (3.5; 17.5), *p* = .004**	**10.9 (4.0; 17.8), *p* = .003**	4.4 (−3.9; 12.7), *p* = .290
MCS	Mental component summary	**9.5 (1.9; 17.1), *p* = .015**	7.3 (−0.4; 15.0), *p* = .061	7.0 (−0.8; 14.8), *p* = .076
PF NBS	Physical functioning	**9.8 (2.9; 16.7), *p* = .007**	**11.3 (5.1; 17.5), *p* = .001**	5.7 (−2.0; 13.4), *p* = .144
RP NBS	Role limitations due to physical health	**9.0 (2.3; 15.7), *p* = .010**	**11.3 (3.0; 19.6), *p* = .009**	4.1 (−3.6; 11.8), *p* = .282
BP NBS	Bodily pain	**12.9 (4.5; 21.2), *p* = .003**	7.7 (−1.6; 17.0), *p* = .102	6.3 (−3.1; 15.7), *p* = .184
GH NBS	General health	**10.8 (2.8; 18.9), *p* = .010**	8.1 (−0.7; 16.2), *p* = .052	6.1 (−3.2; 15.3), *p* = .192
VT NBS	Vitality	**11.1 (4.4; 17.8), *p* = .002**	6.6 (−1.5; 14.6), *p* = .107	5.9 (−2.5; 14.3), *p* = .162
SF NBS	Social functioning	**11.1 (3.4; 18.8), *p* = .006**	**9.2 (1.7; 16.7), *p* = .017**	4.4 (−4.0; 12.8), *p* = .294
RE NBS	Role emotional	**9.6 (1.6; 17.7), *p* = .020**	**12.7 (4.3; 21.0), *p* = .004**	**11.9 (3.3; 20.5), *p* = .008**
MH NBS	Mental health	**11.0 (4.0; 18.1), *p* = .003**	4.5 (−3.2; 12.1), *p* = .243	3.7 (−4.2; 11.6), *p* = .347

RNFL: retinal nerve fibers thickness.
$p < .05$ was considered significant (bold figures).

pathway. In 14/54 (26%) right eyes and 15/54 (28%) left eyes with the most severe damage, the amplitude was not measurable because the evoked visual potentials could not be elicited, and in only 6/54 (11%) of right eyes and 9/54 (17%) of left eyes was an abnormal VEP amplitude detected.

The effect of long-term visual sequelae of methanol poisoning, namely abnormal RNFL thickness, on the follow-up quality of life of survivors is presented in Table 5. All scores were significantly lower in the patients with abnormal RNFL findings, compared to those with normal findings, on the first examination. The difference in the scores between the groups with normal and abnormal RNFL thickness, however, gradually decreased with time and became insignificant on the third examination at 6 years post-discharge. Only the RE NBS score remained significantly lower in those with visual sequelae of poisoning.

3.5. Toxic brain lesions, signs of brain hemorrhages on MRI, and quality of life in survivors of acute methanol poisoning

In 53 patients from the study population, brain MRI was performed, and in 1 patient it was contraindicated. Brain lesions were found in 43% of the patients. Of them, 78% had signs of brain hemorrhage on MRI. The association between the presence of brain lesions or brain hemorrhages on MRI imaging and the quality of life during the 6-year observation is presented in Table 6.

The patients with necrotic brain lesions had lower physical and mental scores compared to those without brain lesions, but only the difference in MCS and SF NBS on the first examination was significant. There was no significant difference between the patients with and without brain lesions 6 years post-discharge.

On the other hand, in 18 patients with more severe toxic brain damage, with signs of brain hemorrhages on MRI, the difference in both physical and mental scores was more pronounced on the first examination and remained significant for PCS, BP NBS, and SF NBS on the third examination, or 6 years post-discharge (Table 6).

4. Discussion

At present, no information is available regarding health-related quality of life of survivors of acute methanol poisoning and the impact of long-term health sequelae on their life during the years following discharge. In this study, we report a study that prospectively evaluated 6-year dynamics of quality of life in a cohort of patients after a mass methanol poisoning outbreak and relationships between physical and mental components of quality of life and hospital treatment modalities, severity, and visual and CNS sequelae of poisoning. Our study demonstrated that acute methanol poisoning significantly decreased quality of life in the population of survivors, mainly in PCS and PF scores, compared to age-adjusted controls with chronic alcohol abuse without a history of acute methanol exposure. In more than 40% of survivors of methanol poisoning, signs of severe disability were present, with a slow decline in physical component summary during the 6-year observation. On the other hand, the MCS scores were higher compared to the controls, with positive dynamics in the following years. Damage to the optic nerve, with optic axon demyelination and degeneration, was associated with a significant decrease in both PCS and MCS scores. Interestingly, signs of physical and mental adaptation to long-term visual sequelae of methanol poisoning were registered with a gradual reduction in the difference in most of physical and mental scores between the groups with and without visual sequelae during the 6-year observation. Finally, necrotic brain lesions did not promote physical or mild transient effects on mental components of quality of life of survivors during the follow-up. However, signs of brain hemorrhages, which indicate severe toxic brain damage, were associated with a permanent decrease in the physical component score and certain components of the mental score that were still detectable 6 years after discharge.

During methanol mass poisoning outbreaks, the mortality rate may exceed 30%, and the effect of health sequelae of poisoning on the quality of life of survivors may be considered "of secondary importance." Nevertheless, toxic brain damage and visual loss present a serious challenge for the survivors. The prevalence of visual sequelae of toxic optic neuropathy reaches up to 40%, and chronic retinal

Table 6. Effect of toxic brain lesions and brain hemorrhages on the quality of life of survivors of acute methanol poisoning.

	Linear mixed effect model								
	No brain lesion			Brain lesion			Mean difference, 95%CI, *p*		
Shortcut	1st exam	2nd exam	3rd exam	1st exam	2nd exam	3rd exam	1st exam	2nd exam	3rd exam
PCS	47.7 (43.5;51.9)	47.6 (43.4;51.8)	46.9 (42.2;55.8)	45.8 (41.0;50.6)	44.1 (39.3;48.9)	45.0 (39.1; 48.7)	−1.9 (−8.3; 4.5); $p = .558$	−3.5 (−9.8; 2.8); $p = .281$	−2.6 (−9.1; 3.8); $p = .426$
MCS	50.4 (46.2;54.6)	48.6 (44.4;52.8)	48.6 (45.0;53.3)	43.3 (38.5;48.1)	47.7 (42.8;52.5)	48.7 (43.3; 53.0)	**−7.1 (−13.5; −0.7); $p = .030$**	−1.0 (−7.4; 5.5); $p = .772$	−1.0 (−7.4; 5.4); $p = .767$
PF NBS	48.2 (44.0; 52.3)	40.0 (44.2; 51.9)	47.4 (42.9;51.2)	45.2 (40.5; 49.9)	42.2 (37.9; 46.5)	46.3 (40.2; 49.4)	−3.7 (−9.6; 2.2) $p = .225$	**−5.8 (−11.6; −0.1) $p = .048$**	−2.14 (−8.4; −4.1) $p = .505$
RP NBS	46.9 (42.7;51.1)	48.0 (43.4;52.7)	47.3 (43.2;50.1)	45.9 (41.2;50.5)	44.5 (39.2;49.8)	46.1 (42.3; 51.8)	−1.0 (−7.3; 5.2) $p = .750$	−3.6 (−10.6; 3.5) $p = .320$	−1.7 (−8.2; 4.7) $p = .593$
BP NBS	51.8 (46.8;56.9)	48.3 (43.2;53.5)	47.5 (42.1;52.2)	46.0 (40.4;51.7)	45.8 (40.1;51.6)	45.9 (38.3; 45.8)	−5.8 (−13.4; 1.8) $p = .133$	−2.5 (−10.2; 5.2) $p = .523$	−3.13 (−10.8; 4.5) $p = .422$
GH NBS	45.0 (40.2;49.8)	45.1 (40.5;49.8)	45.5 (40.5;50.1)	42.0 (36.6;47.5)	44.3 (39.1;49.6)	43.7 (37.7; 48.6)	−2.9 (−10.3; 4.3) $p = .422$	−0.8 (−7.8; 6.3) $p = .827$	−2.2 (−9.5; 5.1) $p = .556$
VT NBS	51.1 (46.8;55.3)	51.6 (47.0;56.2)	49.6 (45.5;54.5)	46.3 (41.6;51.0)	50.7 (45.6;55.8)	50.2 (45.3; 55.5)	−4.7 (−11.1; 1.6) $p = .144$	−0.9 (−7.7; 6.0) $p = .801$	0.6 (−6.4; 7.2) $p = .905$
SF NBS	49.1 (44.7;53.5)	47.4 (43.1;51.8)	47.7 (43.2;52.2)	40.7 (35.7;45.7)	44.3 (39.5;49.2)	44.6 (37.5; 48.0)	**−8.4 (−15.1; −1.7) $p = .014$**	−3.1 (−9.6; 3.4) $p = .352$	−3.0 (−11.8; 1.9) $p = .157$
RE NBS	48.9 (44.6;53.6)	45.2 (40.4;50.1)	47.1 (42.2;52.5)	41.9 (36.7;47.2)	43.9 (38.3;49.4)	45.5 (37.9; 49.9)	−7.0 (−14.1; 0.4) $p = .064$	−1.4 (−8.8; 6.0) $p = .711$	−3.5 (−11.4; 4.4) $p = .383$
MH NBS	50.3 (46.0;54.5)	50.1 (46.0;54.3)	48.7 (45.1;53.5)	44.6 (39.8;49.3)	47.0 (42.3;51.6)	50.4 (45.4; 55.0)	−5.7 (−12.0; 0.6) $p = .078$	−3.2 (−9.4; 3.1) $p = .322$	0.9 (−5.4; 7.22) $p = .787$
	Brain hemorrhages						Mean difference, 95%CI, *p*		
	No hemorrhages			Hemorrhages					
	1st exam	2nd exam	3rd exam	1st exam	2nd exam	3rd exam	1st exam	2nd exam	3rd exam
PCS	48.9 (45.2;52.7)	48.7 (45.1;52.3)	48.0 (45.1;52.6)	42.7 (37.3;48.1)	40.7 (35.4;45.9)	40.6 (32.9; 43.7)	−6.2 (−12.8; 0.3) $p = .063$	**−8.0 (−14.4; −1.7) $p = .013$**	**−7.4 (−14.0; −0.6) $p = .033$**
MCS	49.8 (45.9;53.6)	49.0 (45.1;52.8)	49.5 (45.5;52.9)	42.2 (36.6;47.8)	46.7 (41.1;52.3)	46.1 (42.1; 55.5)	**−7.6 (−14.4; −0.8) $p = .041$**	−2.3 (−9.1; 4.5) $p = .507$	−3.4 (−11.4; 3.0) $p = .25$
PF NBS	48.9 (45.2;52.6)	48.2 (44.8;51.6)	48.2 (45.2;51.5)	42.7 (37.4;47.9)	39.9 (35.1;44.7)	43.1 (37.1; 48.4)	−6.2 (−12.7; 0.2) $p = .074$	**−8.3 (−14.2; −2.4) $p = .006$**	−5.1 (−11.8; 1.6) $p = .136$
RP NBS	47.7 (44.0;51.5)	48.2 (44.0;52.4)	48.7 (43.7;51.3)	43.9 (38.6;49.2)	43.0 (37.0;49.0)	41.4 (35.8; 47.9)	−3.8 (−10.4; 2.7) $p = .249$	−5.2 (−12.6; 2.1) $p = .164$	−7.3 (−9.2; 4.7) $p = .06$
BP NBS	52.4 (47.9;56.8)	49.9 (45.3;54.4)	49.1 (44.5;53.3)	43.2 (36.9;49.5)	42.1 (35.7;48.5)	40.4 (32.6; 45.9)	**−9.1 (−16.5; −1.4) $p = .020$**	−7.8 (−15.7; 0.7) $p = .052$	**−8.7 (−17.6; −1.6) $p = .018$**
GH NBS	46.0 (41.7;50.2)	47.2 (43.1;51.3)	46.0 (41.7;50.4)	39.0 (32.8;45.2)	39.9 (34.1;45.8)	41.0 (34.8; 47.8)	−7.0 (−14.5; 0.5) $p = .068$	**−7.2 (−14.4; −0.1) $p = .046$**	−5.0 (−12.5; 3.0) $p = .225$
VT NBS	51.1 (47.3;54.9)	52.3 (48.1;56.4)	51.0 (47.4;55.4)	44.7 (39.3;50.1)	49.1 (43.3;55.0)	46.4 (41.4; 53.7)	−6.4 (−13.0; 0.2) $p = .057$	−3.1 (−10.3; 4.0) $p = .390$	−4,6 (−11.2; 3.4) $p = .303$
SF NBS	49.5 (45.7;53.3)	48.3 (44.5;52.1)	48.5 (44.9;52.7)	37.2 (31.8;42.6)	41.7 (36.3;47.1)	40.3 (32.5; 44.6)	**−12.3 (−18.9; −5.7) $p<.001$**	−6.6 (−13.3; 0.01) $p = .050$	**−8.2 (−17.4; 3.0) $p = .005$**
RE NBS	47.9 (43.6;52.2)	45.9 (41.5;50.3)	48.1 (43.7;52.8)	41.8 (35.6;47.9)	42.0 (35.6;48.4)	41.6 (32.7; 47.3)	−6.1 (−13.7; 1.3) $p = .107$	−3.9 (−11.6; 3.9) $p = .329$	−6.5 (−16.9; 0.3) $p = .058$
MH NBS	50.4 (46.6;54.1)	50.0 (46.1;53.8)	49.6 (46.2;53.8)	42.5 (37.2;47.8)	46.4 (41.0;51.7)	48.9 (43.7; 55.4)	**−7.9 (−14.4; −1.4) $p = .018$**	−3.6 (−10.2; 3.0) $p = .287$	−0.7 (−7.4; 6.5) $p = .901$

$p < .05$ was considered significant (bold figures).

neurodegeneration with progressive optic axonal loss may be registered in up to 25% of the patients [37,38]. This process is associated with progressive loss of visual functions, which will limit the patients in their professional and private life. The patients from our cohort had mean scores of all quality of life components that were lower than 50 points. These data suggest at least mild overall disability compared to common population, with the evidence of severe disability in two out of five patients from the study population. The PCS of controls with chronic alcohol abuse was significantly higher after adjustment for age and gender, with the greatest difference in the PF score. This finding reflects limitations in daily life of methanol poisoning-survivors due to serious health sequelae. On the other hand, the MCS in methanol-exposed patients was higher compared to controls, a result that can be attributed to specific cognitive impairment with decreased criticism and emotional changes due to a disruption of functional architecture of frontostriatal circuitry [25,29]. The effect of mandatory abstinence on the recruited controls treated in addictology department on their mental component summary should also be considered.

The severity of metabolic acidosis, characterized by arterial blood pH at admission, is a known prognostic factor of hospital mortality—but not follow-up mortality—in survivors discharged from hospitals [22,27]. The patients with a higher serum methanol concentration are typically more exposed and more severely poisoned, although the impact of methanol concentration on the outcome remains questionable [39,40]. In our study, we found no effect of acute laboratory parameters of severity of poisoning, arterial blood pH, and serum methanol concentration on the follow-up quality of life of survivors.

Fomepizole and ethanol are two antidotes applied for the treatment of acute methanol poisoning; both block alcohol dehydrogenase and stop formic acid production. Fomepizole is the preferred antidote over ethanol because its pharmacokinetics are more predictable than ethanol, it has a safer side effect profile, it shortens intensive care unit (ICU) and hospital stays, and it can decrease the need for hemodialysis. In our previous study, we did not find any difference in outcome, length of ICU stay, or dialysis between patients treated with fomepizole or ethanol [41]. In the present study, there was no association between the types of antidote applied in the hospital with follow-up quality of life of survivors of methanol poisoning. Therefore, no antidote demonstrated an advantage from the perspective of long-term quality of life; both antidotes can be applied without concerns on grounds of effectiveness.

The role of enhanced elimination in the treatment of acute methanol poisoning is well established. IDH and different CRRT modalities are commonly used. IDH provides faster correction of the acidosis and the quicker removal of the toxic metabolite formic acid compared to CRRT [42,43]. In our previous study, more patients appeared to survive without sequelae and less patients died when IDH was used compared to continuous modalities. However, there were no differences in outcome when correcting for the severity of the poisoning, as primarily defined by the degree of metabolic acidosis. The absence of differences in the long-term follow-up quality of life of survivors of methanol poisoning treated with different hemodialysis modalities demonstrated in our study confirms that the recommendation of "using whatever mode of dialysis available" remains adequate [44].

Brain hemorrhagic lesions are typical findings in survivors of acute methanol poisoning [17,36,45]. In our study population, 18 out of 23 patients with CNS sequelae of poisoning had MRI signs of brain hemorrhages, while 5 patients had more discrete non-hemorrhagic necrotic brain lesions. The patients with brain hemorrhages had a significantly lower PCS score compared to those without hemorrhagic lesions. This difference persisted for at least 6 years of observation. The MCS, also affected by brain hemorrhages, demonstrated certain signs of adaptation over time. Nevertheless, BP and SF scores remained significantly lower in the patients with hemorrhagic brain lesions. Therefore, adaptation of the patients to toxic brain damage with hemorrhagic lesions was slow, and their quality of life remained significantly affected by CNS sequelae of poisoning. These findings indicate that this category of patients are especially suitable for specific medical and psychosocial rehabilitation programs.

5. Strength and limitations

Our study has certain strengths and limitations. The strengths include the prospective longitudinal design with 6-year follow-up and three consecutive rounds of examinations according to the same standardized clinical protocol in the same medical facility. The population of 54 survivors of acute methanol poisoning exposed over a relatively short time during one mass "epidemic," systematically followed at one medical center, represents a sufficient sample size for regression model estimates, but it should be considered as limited. A larger sample size might have provided more significant associations for separate variables and quality of life scores. We did not estimate the effect of possible pre-existing ocular or neurologic diseases on the quality of life of methanol-exposed patients. The 6-year follow-up period provided sufficient time to estimate the long-term dynamics of physical and mental summary scores; therefore, we operated with complete and reliable information on the long-term impact of acute methanol poisoning on the quality of life. We analyzed both the impact of specific variables (severity of poisoning, treatment modalities) and the overall burden of health sequelae of poisoning (hemorrhagic and non-hemorrhagic brain lesions, optic nerve functions, morphological state of ocular retina). However, the SF-36 may not reflect the true impact of the specific cognitive impairment registered in the survivors of methanol poisoning on the MCS. Nevertheless, the SF-36 is still a common, widely used simple and objective tool of measurement of health-related quality of life.

6. Conclusion

Acute methanol poisoning is a severe medical condition with high mortality and morbidity rates. It significantly decreased

health-related quality of life of survivors persisting for at least 6 years post-discharge. The more pronounced decrease in quality of life scores was observed in the patients with signs of hemorrhagic toxic brain lesions on MRI and abnormal RNFL thickness on OCT.

Disclosure statement

The authors report no conflict of interest. The authors alone are responsible for the content and writing of this article. The manuscript has been read and approved by all authors. The authors certify that the submission is not under review at any other publication. The authors certify that the authors have no other submissions and previous reports that might be regarded as overlapping with the current work. The authors declare no financial disclosures.

Funding

This work was supported with the Project 16-27075A of AZV VES 2016 of Ministry of Health and the Projects PROGRES Q25 and Q29, 1st Faculty of Medicine, Charles University in Prague.

References

[1] Blug M, Leker J, Plass L, et al. Methanol generation economics. In: Bertau M, Offermanns H, Plass L, Schmidt F, Wernicke HJ, editors. Methanol: the basic chemical and energy feedstock of the future. Berlin, Heidelberg: Springer; 2017. p. 603–618.
[2] Kemsley J. Methanol's allure. Chem Eng News. 2007;85(49):55–59.
[3] Hovda KE, Hunderi OH, Tafjord AB, et al. Methanol outbreak in Norway 2002-2004: epidemiology, clinical features and prognostic signs. J Intern Med. 2005;258(2):181–190.
[4] Paasma R, Hovda KE, Tikkerberi A, et al. Methanol mass poisoning in Estonia: outbreak in 154 patients. Clin Toxicol. 2007;45(2):152–157.
[5] Zakharov S, Pelclova D, Urban P, et al. Czech mass methanol outbreak 2012: epidemiology, challenges and clinical features. Clin Toxicol. 2014;52(10):1013–1024.
[6] Choi JH, Lee SK, Gil YE, et al. Neurological complications resulting from non-oral occupational methanol poisoning. J Korean Med Sci. 2017;32(2):371.
[7] Ghannoum M, Hoffman RS, Mowry JB, et al. Trends in toxic alcohol exposures in the United States from 2000 to 2013: a focus on the use of antidotes and extracorporeal treatments. Semin Dial. 2014;27(4):395–401.
[8] Hassanian-Moghaddam H, Nikfarjam A, Mirafzal A, et al. Methanol mass poisoning in Iran: role of case finding in outbreak management. J Public Health. 2015;37(2):354–359.
[9] Sanaei-Zadeh H, Zamani N, Shadnia S. Outcomes of visual disturbances after methanol poisoning. Clin Toxicol. 2011;49(2):102–107.
[10] Barceloux DG, Bond GR, Krenzelok EP, et al. American Academy of Clinical Toxicology practice guidelines on the treatment of methanol poisoning. J Toxicol Clin Toxicol. 2002;40(4):415–446.
[11] Brent J, McMartin K, Phillips S, et al. Fomepizole for the treatment of methanol poisoning. N Engl J Med. 2001;344(6):424–429.
[12] Kraut JA, Mullins ME. Toxic alcohols. N Engl J Med. 2018;378(3):270–280.
[13] Desai T, Sudhalkar A, Vyas U, et al. Methanol poisoning: predictors of visual outcomes. JAMA Ophthalmol. 2013;131(3):358–364.
[14] Urban P, Zakharov S, Diblík P, et al. Visual evoked potentials in patients after methanol poisoning. Int J Occup Med Environ Health. 2015;29(3):471–478.
[15] Zakharov S, Kurcova I, Navratil T, et al. Is the measurement of serum formate concentration useful in the diagnostics of acute methanol poisoning? A prospective study of 38 patients. Basic Clin Pharmacol Toxicol. 2015;116(5):445–451.
[16] Zakharov S, Pelclova D, Urban P, et al. Long-term visual damage after acute methanol poisonings: longitudinal cross-sectional study in 50 patients. Clin Toxicol. 2015;53(9):884–892.
[17] Vaneckova M, Zakharov S, Klempir J, et al. Imaging findings after methanol intoxication (cohort of 46 patients). Neuro Endocrinol Letters. 2015;36(8):737–744.
[18] Bezdicek O, Klempir J, Liskova I, et al. Sequelae of methanol poisoning for cognition. Cesk Slov Neurol Neurochir. 2017;77/110(3):320–325.
[19] Galvez-Ruiz A, Elkhamary SM, Asghar N, et al. Visual and neurologic sequelae of methanol poisoning in Saudi Arabia. SMJ. 2015;36(5):568–574.
[20] Reddy NJ, Sudini M, Lewis LD. Delayed neurological sequelae from ethylene glycol, diethylene glycol and methanol poisonings. Clin Toxicol. 2010;48(10):967–973.
[21] Hassanian-Moghaddam H, Pajoumand A, Dadgar SM, et al. Prognostic factors in methanol poisoning. Hum Exp Toxicol. 2007;26(7):583–586.
[22] Paasma R, Hovda KE, Hassanian-Moghaddam H, et al. Risk factors related to poor outcome after methanol poisoning and the relation between outcome and antidotes – a multicenter study. Clin Toxicol. 2012;50(9):823–831.
[23] Zakharov S, Nurieva O, Kotikova K, et al. Positive serum ethanol concentration on admission to hospital as the factor predictive of treatment outcome in acute methanol poisoning. Monatsh Chem. 2017;148(3):409–419.
[24] Chung JY, Ho CH, Chen YC, et al. Association between acute methanol poisoning and subsequent mortality: a nationwide study in Taiwan. BMC Public Health. 2018;18(1):985.
[25] Mana J, Vaneckova M, Klempíř J, et al. Methanol poisoning as an acute toxicological basal ganglia lesion model: evidence from brain volumetry and cognition. Alcohol Clin Exp Res. 2019;43(7):1486–1497.
[26] Nurieva O, Hubacek JA, Urban P, et al. Clinical and genetic determinants of chronic visual pathway changes after methanol-induced optic neuropathy: four-year follow-up study. Clin Toxicol. 2019;57(6):387–397.
[27] Zakharov S, Rulisek J, Hlusicka J, et al. The impact of co-morbidities on a 6-year survival after methanol mass poisoning outbreak: possible role of metabolic formaldehyde. Clin Toxicol. 2019;1.
[28] Nurieva O, Kotikova K, Urban P, et al. Prevalence, dynamics, and biochemical predictors of optic nerve remyelination after methanol-induced acute optic neuropathy: a two-year prospective study in 54 patients. Monatsh Chem. 2016;147(1):239–249.
[29] Peterová K, Brožová H, Klempíř J, et al. Gait and balance impairment after acute methanol poisoning. Basic Clin Pharmacol Toxicol. 2018;122(1):176–182.
[30] Ware JE, Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). Conceptual framework and item selection. Med Care. 1992;30(6):473–483.
[31] Zakharov S, Pelclova D, Urban P, et al. Use of out-of-hospital ethanol administration to improve outcome in mass methanol outbreaks. Ann Emerg Med. 2016;68(1):52–61.
[32] Rulisek J, Balik M, Polak F, et al. Cost-effectiveness of hospital treatment and outcomes of acute methanol poisoning during the Czech Republic mass poisoning outbreak. J Crit Care. 2017;39:190–198.
[33] Kraut JA, Kurtz I. Toxic alcohol ingestions: clinical features, diagnosis, and management. CJASN. 2008;3(1):208–225.
[34] Mégarbane B, Borron SW, Baud FJ. Current recommendations for treatment of severe toxic alcohol poisonings. Intensive Care Med. 2005;31(2):189–195.
[35] McMartin K, Jacobsen D, Hovda KE. Antidotes for poisoning by alcohols that form toxic metabolites. Br J Clin Pharmacol. 2016;81(3):505–515.
[36] Zakharov S, Kotikova K, Vaneckova M, et al. Acute methanol poisoning: prevalence and predisposing factors of haemorrhagic and

non-haemorrhagic brain lesions. Basic Clin Pharmacol Toxicol. 2016;119(2):228–238.

[37] Nurieva O, Diblik P, Kuthan P, et al. Progressive chronic retinal axonal loss following acute methanol-induced optic neuropathy: four-year prospective cohort study. Am J Ophth. 2018;191: 100–115.

[38] Bezdicek O, Michalec J, Vaneckova M, et al. Cognitive sequelae of methanol poisoning involve executive dysfunction and memory impairment in cross-sectional and long-term perspective. Alcohol. 2017;59:27–35.

[39] Hovda KE, Hunderi OH, Rudberg N, et al. Anion and osmolar gaps in the diagnosis of methanol poisoning: clinical study in 28 patients. Intensive Care Med. 2004;30(9):1842–1846.

[40] Hassanian-Moghaddam H, Zamani N, Roberts DM, et al. Consensus statements on the approach to patients in a methanol poisoning outbreak. Clin Toxicol. 2019;57(12):1129–1136.

[41] Zakharov S, Pelclova D, Navratil T, et al. Fomepizole versus ethanol in the treatment of acute methanol poisoning: comparison of clinical effectiveness in a mass poisoning outbreak. Clin Toxicol. 2015;53(8):797–806.

[42] Zakharov S, Pelclova D, Navratil T, et al. Efficiency of acidemia correction on intermittent versus continuous hemodialysis in acute methanol poisoning. Clin Toxicol. 2017;55(2):123–132.

[43] Zakharov S, Pelclova D, Navratil T, et al. Intermittent hemodialysis is superior to continuous veno-venous hemodialysis/hemodiafiltration to eliminate methanol and formate during treatment for methanol poisoning. Kidney International. 2014;86(1):199–207.

[44] Roberts DM, Yates C, Megarbane B, et al. Recommendations for the role of extracorporeal treatments in the management of acute methanol poisoning: a systematic review and consensus statement. Crit Care Med. 2015;43(2):461–472.

[45] Aisa TM, Ballut OM. Methanol intoxication with cerebral hemorrhage. Neurosciences. 2016;21(3):275–277.