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ORIGINAL ARTICLE

Worse health-related quality of life, impaired functioning and psychiatric comorbidities are associated with excess mortality in patients with severe chronic pain

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Abstract

Background: Severe chronic pain that interferes with daily activities is associated with an increased risk of mortality. We assessed the overall mortality of tertiary chronic pain patients in comparison with the general population, with a special aim to analyse the association of health-related quality of life (HRQoL) and its dimensions with the risk of death.

Methods: In this prospective observational follow-up study, patients with non-cancer chronic pain attended an outpatient multidisciplinary pain management (MPM) episode in a tertiary pain clinic in 2004–2012 and were followed until May 2019. Mortality between the patients and the general population was compared with standardized mortality ratios (SMR) in different age groups. Causes of death and comorbidities were compared among the deceased. Association of mortality and HRQoL and its dimensions, measured with the 15D instrument, was studied with Cox proportional hazards model.

Results: During a mean of 10.4-year follow-up of 1498 patients, 296 died. The SMR in the youngest age group (18–49 years) was significantly higher than that of the general population: 2.6 for males and 2.9 for females. Even elderly females (60–69 years) had elevated mortality (SMR 2.3). Low baseline HRQoL at the time of MPM, as well as poor ratings in the psychosocial dimensions of HRQoL, was associated with an increased risk of death.

Conclusions: Our results support the role of HRQoL measurement by a validated instrument such as the 15D in capturing both the physical and the psychological symptom burden, and consequently, an elevated risk of death, in patients with chronic pain.

Significance: Severe chronic pain is associated with elevated mortality. In patients in chronic pain under 50 years old, the mortality was 2.5–3 times higher than in the general population. Psychological distress appears to contribute to the increased mortality. Regular follow-up by health-related quality of life (HRQoL) measurement could be useful in identifying patients in chronic pain who are in need of intensive symptom management and to prevent early death.

1 | INTRODUCTION

Chronic pain is associated with poor self-rated health and low health-related quality of life (HRQoL) (Breivik et al., 2006; Eriksen et al., 2003; Vartiainen et al., 2016). Evidence consistently shows that mortality is higher in patients with severe chronic pain than in the general population (Macfarlane et al., 2017; Smith et al., 2014; Vaegter et al., 2019). The experience of chronic pain per se is not associated with excess mortality (Andorsen et al., 2016; Åsberg et al., 2016; Macfarlane et al., 2007), but an increased risk of death is seen when chronic pain is either severe (Torrance et al., 2010) or interferes with daily life and physical functioning (Macfarlane et al., 2017; Smith, Wilkie, Croft, Parmar, et al., 2018). Pain interference is not simply a measure of pain intensity since patients with all levels of pain intensity may report that pain interferes with psychological or physical well-being (Jordan et al., 2019). Also, a higher number of pain sites have been associated with the risk of death (McBeth et al., 2008; Nitter & Forseth, 2013), although this association has been inconsistent (Smith, Wilkie, Croft, & McBeth, 2018).

The relationship between chronic pain and excess mortality is complex. Adverse lifestyle factors, such as overweight, poor diet, smoking, physical inactivity, sleep disturbances and substance abuse disorders have been identified as possible mediators between pain and mortality (Andersson, 2009; Macfarlane et al., 2017; Owen-Smith et al., 2019; Smith, Wilkie, Croft, Parmar, et al., 2018). In support of the relevance of lifestyle factors, cardiovascular risk factors and metabolic syndrome are highly prevalent in patients with chronic pain (Goodson et al., 2013), and chronic pain patients' excess mortality from cardiovascular diseases has emerged in several studies worldwide (Fayaz et al., 2016; Macfarlane et al., 2017; Torrance et al., 2010; Vaegter et al., 2019). Even cancer mortality, less obviously explained by lifestyle factors, is higher in chronic pain patients than in the general population (Torrance et al., 2010; Vaegter et al., 2019).

The role of psychological vulnerability factors, such as depression, anxiety and sleep disturbance, as mediators of the excess mortality of chronic pain patients, remains unclear. Psychosocial factors modify pain interference (Jordan et al., 2019; Miettinen et al., 2019). In the general population, the intensity of psychosocial distress is related to excess mortality (Puustinen et al., 2011; Russ et al., 2012), and depression increases the risk of coronary events (Nicholson et al., 2006) and is associated with a higher incidence and increased mortality of cancer (Chida et al., 2008; Pinquart & Duberstein, 2010). Furthermore, depression and anxiety are among the factors increasing the probability of being prescribed opioids for pain management (Quinn et al., 2017). Long-term opioid treatment is a well-known risk factor for increased all-cause mortality (Ray et al., 2016; Solomon, 2010). Other suggested determinants of elevated mortality risk include dysfunction of the stress system as such or as a consequence of long-term opioid use and early life adversities such as childhood abuse or domestic violence (Chen et al., 2016; Koob, & Kreek, 2007; Lee & Ryff, 2019; Valentino & Van Bockstaele, 2015).

We aimed to assess the overall mortality of chronic pain patients compared with the general population and the association of HRQoL and its dimensions on the risk of death. Secondary aims were to report causes of death and to compare the patients who deceased at different ages.

2 | METHODS

2.1 | Study subjects

All patients referred to the pain clinic for multidisciplinary pain management (MPM) between 2004 and 2012 were offered the possibility to participate in a HRQoL follow-up, the only exclusion criterion being active cancer. Before the start of the outpatient MPM episode, the patients received a letter of invitation to participate in a study assessing health-related quality of life (HRQoL) at baseline and follow-up. All patients agreeing to participate gave their written informed consent on their first visit to the pain clinic. The study was approved by the Ethics Committee of the Helsinki University Hospital (§121/09). The demographics of the patients and the HRQoL follow-up results have been reported previously (Vartiainen et al., 2016, 2019).

Of the 1573 patients who agreed to participate in the study and were originally given the 15D HRQoL questionnaire at baseline, 21 were found to have been re-referred to a second MPM treatment episode during follow-up, and these patients were excluded. A further 24 patients were excluded because they returned empty 15D questionnaires at baseline. Thirteen patients were found to have active cancer before the end of MPM and were excluded, and 17 patients were younger than 18 years at baseline and were excluded (none of them had died during the mortality follow-up). The final number of patients in the mortality follow-up was 1498. The flowchart of patient selection is shown in Figure S1.

2.2 | Study setting and follow-up

At the start of MPM, i.e. at baseline, the patients filled in the standard preadmission questionnaire of the pain clinic, used in research and clinical practice in Finland (Knaster et al., 2012), and containing questions about the

patients' socioeconomic background as well as the nature, intensity and interference of pain. In addition, the patients filled in the 15D questionnaire at baseline and 12 months after the start of treatment.

On 22 May 2019, we identified the patients who had died before this date by searching the Finnish population registry. Death during follow-up was coded as a dichotomous variable (0/1), and the follow-up time, i.e. the time between the start of treatment and death or the end of follow-up (22.5.2019), was recorded in days. For mortality comparisons, the patients were allocated to the following groups according to their age at baseline: 18–49 years; 50–59 years; 60–69 years and 70+ years.

The underlying causes of death and the sequence of conditions directly leading to death were collected from the death certificates in the Statistics Finland civil registration records. For the deceased, we collected the causes of death, which are coded using the ICD-10 classification. Statistics Finland (Statistics Finland, 2020) provides data on the life span and causes of death of the Finnish population.

2.3 | Measures

2.3.1 | Pain-related variables

Pain interference, defined as pain that interferes with normal daily activities (Thomas et al., 2004), was measured using the sum score of the question 'How much does your pain affect the following activities?', listing 18 activities with the response options 'not at all,' 'moderately' and 'much'. The respective choices were scored as 0, 1 or 2 points. The sum score was presented as a percentage of the maximum score of 36 points. To eliminate the confounding effect of missing answers on single activities, the sum score was presented as a percentage of an individual patient's theoretical maximum sum score. In other words, we used personal mean imputation to predict the missing answers to the question if the patient had answered at least five of the 18 activities (e.g. if a patient had answered 'moderately' to 17 activities and left 1 activity blank, the patient would have a score of 17 out of 34). Pain intensity and pain-related distress were measured on a VAS scale (0 to 100 mm). The measures are described in detail in the earlier reports of the HRQoL follow-up of the patients (Vartiainen et al., 2016, 2019).

2.3.2 | 15D, the health-related quality-of-life instrument

The 15D is a generic, self-administered, standardized HRQoL instrument (Sintonen, 2001) (www.15d-instrument.net). It consists of 15 dimensions of health (mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality and sexual activity), each having five levels of severity from which the patient chooses the one best describing his/her health state at that moment. It takes about 5 min to fill in the questionnaire. The 15D can be used both as a profile and as a single index score measure.

The single index number (15D score) represents the overall HRQoL on a scale of 0 to 1, where 0 = death and 1 = full health. The individual dimension level values reflect the seriousness of problems in each dimension on a 0–1 scale (0 = death; 1 = no problems). Mean dimension level values are used to draw the 15D profiles.

The scores are calculated from the health state descriptive system (questionnaire) by using a set of population-based preference or utility weights. These weights have been elicited from representative Finnish population samples by using magnitude estimation in a three-stage valuation process based on the multi-attribute utility theory (Sintonen, 2001). Thus, the scores reflect the population's preferences of a certain health state over death and full health.

Clinically important changes of the 15D score have been established using an anchor-based method: a change ≥0.015 (positive or negative) is considered to indicate a clinically important improvement or deterioration and a change >0.035 to indicate a major improvement or deterioration (Alanne et al., 2015). The 15D has been shown to be valid in patients with chronic pain (Vartiainen et al., 2017).

2.3.3 | Comorbidity

Data on comorbidities at the start of MPM were retrieved from the Helsinki University Hospital medical records by manually screening the patient charts, referrals and diagnoses at the start of MPM. To classify these medical comorbidities, we calculated the Charlson Age Comorbidity Index (CACI) (Charlson et al., 1987) for each deceased patient. The CACI is a method for classifying comorbid conditions that might alter the risk of death in longitudinal studies. Each of the 19 comorbid conditions has been assigned a weighted number from 1 to 6, with each decade over the age of 40 contributing 1 point to the score. A higher number represents an increased comorbidity score, and consequently, a higher risk of death. CACI is the most studied and well-validated method for quantifying comorbid conditions (Degroot et al., 2003; Quan et al., 2011). We also reported the Charlson Comorbidity Index (CCI) Score without age, where the contribution of age is removed, to illustrate the comorbidities.

2.4 | Statistical analyses

The descriptive statistics are presented as means with standard deviations (SD) or counts with percentages. Comparisons among groups were done with the Student's *t*-test or ANOVA for continuous variables and the chi-square test for categorical variables. In the case of violation of the assumptions (e.g. non-normality) for continuous variables, a bootstrap-type method or Monte Carlo *p*-values (small number of observations) for categorical variables were used. Cumulative mortality was estimated with the Kaplan–Meier's method and compared between groups with the log-rank test. Cox proportional hazards regression was used to estimate the adjusted hazard ratios (HR) and their 95% confidence intervals (CIs). A possible non-linear relationship between the 15D score and the hazard of death was assessed by using the 4-knot-restricted cubic spline Cox proportional hazards model. The knots were located at the 5th, 35th, 65th and 95th percentiles, based on Harrell's recommended percentiles (Harrell, 2001). Standardized mortality ratios (SMRs) were used to quantify the risk of death in this cohort compared with the general population. The ratio of observed to expected number of deaths, i.e. the standardized mortality ratio (SMR) for all-cause mortality, was calculated using subject-years methods with 95% confidence intervals (CI). The expected number of deaths was calculated on the basis of sex-, age- and calendar period-specific mortality rates in the Finnish population (Statistics Finland, 2020). The expected number was determined by multiplying the person-years of observation by the appropriate mortality rate in the general population according to categories of sex, 1-year age group and calendar period. Ninety-five percent confidence intervals (95% CI) were computed by assuming that the observed number of deaths followed a Poisson distribution. Statistical evaluation of SMRs was made with the Poisson regression models. The Poisson regression models were tested using the goodness-of-fit test and the assumptions of overdispersion in models were tested using the Lagrange multiplier test. Correlation coefficients were calculated by using the Spearman method. Stata 17.0 (StataCorp LP) statistical package was used for the analysis.

3 | RESULTS

3.1 | Patient characteristics

The mean length of follow-up was 10.4 (SD 3.2) years. During that time, 296 (19.5%) of the 1498 study patients had died at a mean age of 73.1 (SD 14.3) years. Characteristics of the study patients are shown in Table 1 according to the age at the start of MPM. Table 2 shows the deceased patients' comorbid diseases at baseline.

3.2 | Causes of death

The causes of death are classified according to the Statistics Finland ICD-10 main categories, and they are shown in Table 3.

3.3 | Standardized mortality ratios

The mortality of the study subjects was compared with that of the general population by calculating standardized mortality ratios (SMR). Overall SMR for females was 1.63 (95% CI −1.40–1.90) and for males 1.46 (95% CI 1.23–1.74). The SMRs according to the age groups are shown in Figure 1. The excess mortality was most pronounced in the youngest patients: For the age group 18–49 years, the SMR was 2.9 (95% CI 1.8–4.6) for females and 2.6 (95% CI 1.7–4.1) for males. In females, the mortality was also elevated in the age group 60–69 (SMR 2.3, 95% CI 1.7–3.2), whereas in males aged 60–69, the SMR was not statistically significantly different from that of the general population. In males, there was a linear relationship between age and SMR (Figure 1).

3.4 | The association of HRQoL and the risk of death

We analysed the association of the baseline 15D HRQoL score as well as the 15D dimensions with the hazard of death by using age- and gender-adjusted Cox proportional hazards models. An increase of the baseline 15D score by 1 SD (+0.114) was associated with a linear reduction in the hazard of death to 0.68 (95% CI 0.61–0.76).

In the deceased patients, the baseline 15D score was not correlated with the CACI score (Spearman's rho = −0.05, $p = 0.422$). In the CCI score without the effect of age, the correlation with the 15D score was statistically significant but small (Spearman's rho = −0.13, $p = 0.02$).

We analysed the association of the baseline 15D dimension scores with the hazard of death. Figure 2 shows the results of multiple parallel age- and sex-adjusted Cox proportional hazard models with the standardized z-scores of the 15D dimensions as predictors. A decrease in the hazard ratio (HR) associated with a decrease of −1SD in severity of symptoms was seen in the following dimensions (numbers indicate the HR with respective 95% CI; hazard ratios are decreasing because a higher score indicates less

TABLE 1 Patient characteristics of the patients

	Age at baseline, years			
	18–49	**50–59**	**60–69**	**70+**
n	611	353	260	274
Female gender, *n* (%)	386 (63.2)	206 (58.4)	166 (63.8)	186 (67.9)
Duration of pain >3 years, *n* (%)	127 (24.7)	68 (24.5)	48 (22.6)	58 (25.8)
Currently actively working, *n* (%)	215 (38.5)	100 (30.8)	30 (12.4)	5 (2.0)
Pain intensity VAS, mean (SD)	57.1 (24.8)	62.7 (22.3)	61.1 (23.9)	63.5 (26.5)
Pain-related distress VAS, mean (SD)	72.5 (26.1)	73.9 (24.1)	67.4 (24.8)	70.2 (25.9)
Pain interference %, mean (SD)	58.6 (20.8)	64.0 (19.9)	59.7 (21.0)	62.4 (22.2)
15D HRQoL score, mean (SD)	0.722 (0.113)	0.696 (0.115)	0.717 (0.111)	0.694 (0.118)
Crude mortality descriptive statistics				
Deaths during follow-up, *n* (%)	34 (5.6)	40 (11.3)	70 (26.9)	152 (55.5)
Follow-up time, days, mean (SD)	3935 (944)	3831 (1041)	3536 (1207)	2888 (1333)
Person-years followed	6580	3701	2516	2166
Death rate during follow-up (deaths/year/100,000 persons)	517	1081	2782	7019

Note: Baseline variables are shown according to the age at the start of the multidisciplinary pain management episode.

Abbreviations: HRQoL, health-related quality of life; SD, standard deviation; VAS, visual analogue scale (0–10).

severe symptoms): Breathing (0.66, 0.60–0.74); mobility (0.70, 0.62–0.79); usual activities (0.73, 0.65–0.82); discomfort and symptoms (0.76, 0.67–0.86); sexual activity (0.81, 0.72–0.91); eating (0.81, 0.74–0.88); vitality (0.84, 0.75–0.95); vision (0.84, 0.77–0.92); distress (0.85, 0.75–0.95) and sleeping (0.88, 0.79–0.99). All HRs are adjusted for age and gender, not for other dimensions.

Figure 3 shows the association between the baseline 15D score and the hazard of death in an age- and gender-adjusted restricted cubic splines Cox proportional hazards model, where we compared the increase or decrease of the hazard ratio of death relative to the median (0.717) of the 15D score. There was a strong increase in the hazard of death associated with the decrease in the 15D score. However, an increase in the baseline 15D score was associated with a less clear, not statistically significant decrease in the hazard of death.

4 | DISCUSSION

Our results agree with previous studies, which have shown that severe pain or pain interfering with daily life is associated with increased mortality (Macfarlane et al., 2017; McBeth et al., 2008; Smith et al., 2003; Smith, Wilkie, Croft, Parmar, et al., 2018; Torrance et al., 2010; Zhu et al., 2007).

In our study, the all-cause mortality compared with that in the general population was elevated in younger patients – in the age group of 18–49 years; the mortality was 2.5–3-fold. In females aged 60–69 years, the all-cause mortality was 2.5-fold, whereas in males of similar age and in the oldest age group, the mortality was not different from that of the general population. The oldest group of deceased had had less depression and anxiety and significantly less other psychiatric diagnoses and substance use disorders at baseline than the younger age groups. Taken together, these older patients may have had less psychological distress, which has been shown to associate with an increased risk of mortality (Nitter & Forseth, 2013; Russ et al., 2012).

Most studies on chronic pain and mortality have been population based (Andorsen et al., 2016; Åsberg et al., 2016; Macfarlane et al., 2017; Nitter & Forseth, 2013; Smith, Wilkie, Croft, & McBeth, 2018; Smith, Wilkie, Croft, Parmar, et al., 2018). A study from a multidisciplinary pain clinic in Denmark reported in their patients a six-fold higher mortality rate than in the general population (Vaegter et al., 2019). Population studies and studies on specific chronic pain patients, such as ours and those of others (Dreyer et al., 2010; Krause et al., 2017; Vaegter et al., 2019; Wolfe et al., 2011) probably represent different ends of the spectrum of patients with long-lasting pain, which could explain why some previous studies did not show any relationship between pain and mortality (Andorsen et al., 2016; Åsberg et al., 2016). In our study of tertiary MPM patients, the overall SMR was not as high as in Denmark, but we showed a strong association of HRQoL and its psychosocial problems with overall mortality.

TABLE 2 The baseline comorbidity data on the deceased patients. The deceased were allocated into groups according to their age at baseline

Variable	Age at baseline, years				
	18–49	50–59	60–69	70+	*p*
Baseline 15D HRQoL score, mean (SD)	0.703 (0.105)	0.635 (0.120)	0.687 (0.118)	0.667 (0.122)	0.057
15D HRQoL score change at 12 months, mean (SD)	0.003 (0.086)	0.017 (0.081)	−0.003 (0.086)	−0.010 (0.093)	0.602
Charlson comorbidity index (CCI)					
CCI disease score, mean (SD)	1.0 (1.4)	1.6 (1.45)	1.7 (1.4)	1.5 (1.4)	0.114
Myocardial infarction	<5	<5	6 (8.6)	15 (9.9)	0.489
Heart failure	<5	<5	6 (8.6)	18 (11.9)	0.281
Atherosclerosis	<5	8 (20.0)	10 (14.3)	26 (17.2)	0.159
Cerebrovascular disease	0 (0.0)	7 (17.5)	9 (12.9)	25 (16.6)	0.076
Hemiplegia	0 (0.0)	<5	<5	5 (3.3)	0.761
Cognitive impairment	0 (0.0)	0 (0.0)	<5	7 (4.6)	0.306
Respiratory disease	<5	8 (20.0)	12 (17.1)	28 (18.5)	0.149
Inflammatory condition	3 (8.8)	<5	13 (18.6)	24 (15.9)	0.306
Peptic ulcer	<5	0 (0.0)	<5	9 (6.0)	0.327
Local neoplasm	<5	<5	6 (8.6)	11 (7.3)	0.680
Leukaemia	<5	<5	<5	<5	0.571
Lymphoma	0 (0.0)	0 (0.0)	<5	<5	0.779
Chronic kidney disease	5 (14.7)	<5	5 (7.1)	7 (4.6)	0.182
HIV	0 (0.0)	<5	0 (0.0)	0 (0.0)	0.094
Diabetes	6 (17.6)	8 (20.0)	15 (21.4)	23 (15.2)	0.694
Liver disease	<5	0 (0.0)	6 (8.6)	<5	0.083
Other conditions, not included in the CCI					
Depression	12 (36.4)	13 (37.1)	12 (18.5)	26 (18.7)	0.024
Anxiety disorder	8 (24.2)	6 (17.1)	5 (7.7)	9 (6.5)	0.010
Substance abuse or addiction	10 (30.3)	7 (20.0)	10 (15.4)	7 (5.0)	<0.001
Other psychiatric diagnosis	14 (42.4)	10 (28.6)	14 (21.5)	10 (7.1)	<0.001
Opioid use over 6 months after baseline	26 (78.8)	28 (80.0)	44 (67.7)	82 (59.0)	0.035

Note: p value shows the statistical significance of the difference between the groups. Values listed are counts and percentages, if not otherwise stated. If there were <5 individuals in a group, we show "<5" to preserve the confidentiality of the patients.

Abbreviations: CCI, Charlson Comorbidity Index (without age); HIV; HRQoL, health-related quality of life; Human Immunodeficiency Virus.

Worse baseline HRQoL was very clearly associated with mortality (Figure 3). In the general population, a similar association between higher HRQoL and lower all-cause mortality risk has been reported (Phyo et al., 2020), and the interference of chronic pain with daily life is associated with elevated mortality (Macfarlane et al., 2017; Smith, Wilkie, Croft, Parmar, et al., 2018). P sychosocial and functional dimensions of HRQoL (discomfort and symptoms, distress, mobility, sexual activity, vitality and usual activities) were clearly associated with the hazard of death. They are also the dimensions where pain patients with chronic pain report the most severe symptoms compared to the general population (Vartiainen et al., 2017). Supporting the importance of psychosocial factors, the 15D HRQoL score at baseline did not correlate with the CACI score and was strongly associated with pain interference in our previous study (Vartiainen et al., 2016). It should be noted that multimorbidity is associated with worse HRQoL (Makovski et al., 2019), and comorbid conditions at baseline, other than the exclusion of active cancer, were not analysed in this study.

A high burden of chronic pain may manifest in, for example, difficulties in maintaining a healthy lifestyle or delays in seeking medical treatment for disease symptoms. Cardiovascular- and cancer-related mortality is elevated in the chronic pain population (Fayaz et al., 2016; Macfarlane et al., 2017; Torrance et al., 2010; Vaegter et al., 2019). Poor diet, overweight, low levels of physical activity

TABLE 3 The causes of death according to the ICD-10 disease classification of the underlying cause of death

	Age at baseline, years				
	18–49	50–59	60–69	70+	Total
N	37	48	62	149	296
Causes of death, *n* (%)					
Infectious diseases	0 (0)	<5	0 (0)	<5	4 (1)
Neoplasms	7 (19)	10 (21)	17 (27)	29 (19)	63 (21)
Diseases of the blood (e.g. haematologic malignancies)	0 (0)	0 (0)	<5	0 (0)	<5
Endocrine, nutritional and metabolic diseases	<5	0 (0)	<5	<5	6 (2)
Mental and behavioural disorders	<5	<5	0 (0)	<5	6 (2)
Diseases of the nervous system	0 (0)	3 (6)	8 (13)	15 (10)	26 (9)
Dementias	0 (0)	1 (2)	5 (11)	15 (10)	21 (7)
Diseases of the circulatory system	<5	17 (35)	21 (34)	59 (40)	100 (34)
Diseases of the respiratory system	5 (14)	5 (10)	6 (10)	12 (8)	28 (9)
Diseases of the digestive system	<5	2 (4)	2 (3)	8 (5)	15 (5)
Diseases of the skin and subcutaneous tissue	0 (0)	0 (0)	0 (0)	<5	<5
Diseases of the musculoskeletal system and connective tissue	0 (0)	<5	<5	<5	<5
Diseases of the genitourinary system	0 (0)	0 (0)	<5	<5	4 (1)
Congenital malformations, deformations and chromosomal abnormalities	0 (0)	<5	0 (0)	0 (0)	<5
External causes of mortality (e.g. traumas)	15 (41)	5 (10)	3 (5)	10 (6)	33 (11)
Suicides	<5	<5	0 (0)	0 (0)	6 (2)
Intoxications involving alcohol	<5	<5	0 (0)	0 (0)	6 (2)

Note: The patients were allocated into age groups according to the age at death. If there were <5 individuals in a group, we show "<5" to preserve the confidentiality of the patients.

and smoking have consistently been concluded to mediate the relationship between chronic pain and excess mortality (Andersson, 2009; Macfarlane et al., 2017; Owen-Smith et al., 2019; Smith, Wilkie, Croft, Parmar, et al., 2018). These lifestyle factors are also associated with decreased HRQoL (Ford et al., 2014; Lau et al., 2021; Stephenson et al., 2021; Vogl et al., 2012). Since poor lifestyle habits are common in chronic pain patients also in Finland (Shiri et al., 2020), they probably mediate the association of HRQoL and mortality also in the present study population.

Prescription opioid use in chronic pain has a negative effect on HRQoL (Dick et al., 2011) and significantly increases the risk of death (Ekholm et al., 2014; Krause et al., 2017; Ray et al., 2016; Zeng et al., 2019). Females, but not males, using opioids are at elevated risk of cardiovascular death (Khodneva et al., 2015). The proportion of opioid users among our patients (58%) was close to that of another study from a tertiary pain clinic (Dick et al., 2011), but especially younger deceased patients had very high rates (80%) of long-term opioid use. It is possible that opioid use was at least a contributory factor to the death of patients in chronic pain. However, we were unable to access data on opioid use immediately prior to death and what part they played in the intoxications.

Affective symptoms are prevalent in chronic pain (Arola et al., 2010; Barry et al., 2013) and have been shown to act as mediators between chronic pain and poor HRQoL (Vartiainen et al., 2016) and also between pain and suicidal behaviour (Jacob et al., 2018; Owen-Smith et al., 2019). Chronic pain is an independent risk factor of suicidality (Campbell et al., 2015; Ilgen et al., 2013; Owen-Smith et al., 2019; Racine, 2018), but pain-related risk factors for suicide are not as well-established. Patients with painful fibromyalgia are at increased risk of death by suicide, although this patient group does not seem to have an increase in overall mortality (Dreyer et al., 2010; Wolfe et al., 2011). In the present study, both suicides and intoxications with unknown intentionality occurred in the youngest age groups, as in the general population (Statistics Finland, 2020). Psychiatric diagnoses, both depression, anxiety and

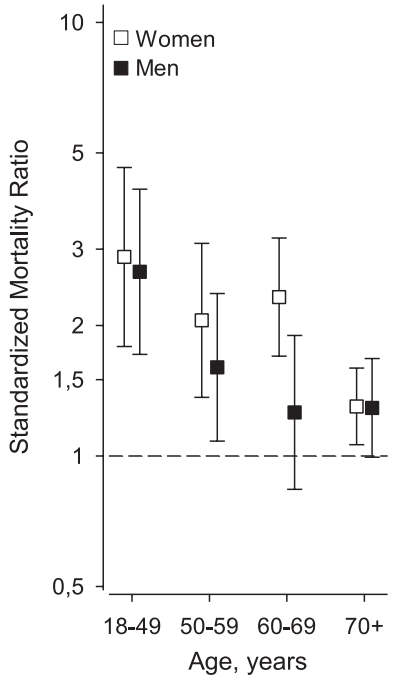

FIGURE 1 The standardized mortality ratios according to the age groups. For the age group 18–49 years, the SMR was 2,9 for females and 2,6 for males. Note the logarithmic scale of the y-axis. The *p* for linearity of the SMRs according to the age groups for females and males was 0.049 and 0.007, respectively

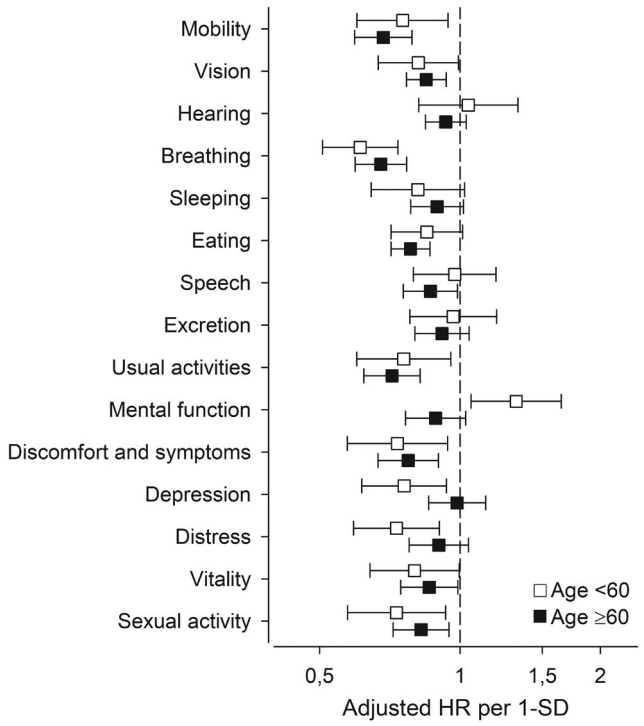

FIGURE 2 The association of the symptoms in 15D dimensions and the hazard of death in two groups, <60 years old and >= 60 years old according to the age at baseline. All dimension scores are standardized to z-scores of the whole study sample for comparability. An increasing dimension score indicates less severe symptoms in the 15D. If the confidence interval of HR is below 1, it indicates that worse symptoms in the dimension are associated with statistically significant increase in the risk of death. HRs are obtained from parallel age- and gender-adjusted Cox proportional hazard models with each individual dimension as a predictor variable. In other words, the models are not adjusted for other dimensions, and the age adjustment is done inside the two age groups. HR, hazard ratio

others, were more common in this age group. Accordingly, depression and distress were more clearly and statistically significantly associated with mortality in those <60 years (Figure 2). Psychosocial factors are associated with higher pain interference (Barry et al., 2013; Jordan et al., 2019; Scott et al., 2016), and a linear association between increasing pain interference and suicidal behaviour has been shown (Blakey et al., 2018; Jacob et al., 2018). It is possible that those patients in chronic pain who are at risk of suicide represent a subset of chronic pain patients with more challenging psychiatric comorbidities that have either not been diagnosed or treated. Possible mediators in the association of mortality, suicidality and psychosocial aspects of chronic pain include dysfunction of the stress system as such or as a consequence of long-term opioid use, as well as early life adversities and traumatic experiences (Chen et al., 2016; Koob, & Kreek, 2007; Lee & Ryff, 2019; Valentino & Van Bockstaele, 2015).

These findings support the role of HRQoL measurement by 15D in capturing, in addition to comprehensive symptom burden, also the risk for death of these patients. Regular HRQoL measurements with a validated instrument (such as the 15D) in long-term follow-up of chronic pain patients could prove useful in identifying patients needing different or more intensive treatment approaches and also in preventing excess mortality of these burdened patients.

4.1 | Strengths and limitations

The strength of our study is the large number of patients from a tertiary pain clinic. We used standardized mortality ratios to compare the rate of death to that in the general population. We used robust and carefully planned statistical methods in analysing the association of HRQoL and its dimensions with mortality. Medical comorbidities were reported by using a validated classification method, although only for deceased patients. However, this is a prospective follow-up study. The study subjects represent the most difficult and severe cases of the large and diverse population of patients in chronic pain, and our results may not fully represent e.g. those in primary care. Furthermore, we compare the patients in chronic pain to the general population as a single group, and it is likely that the present analyses miss potentially important subgroups (such as those who have experienced early life adversities) inside the very

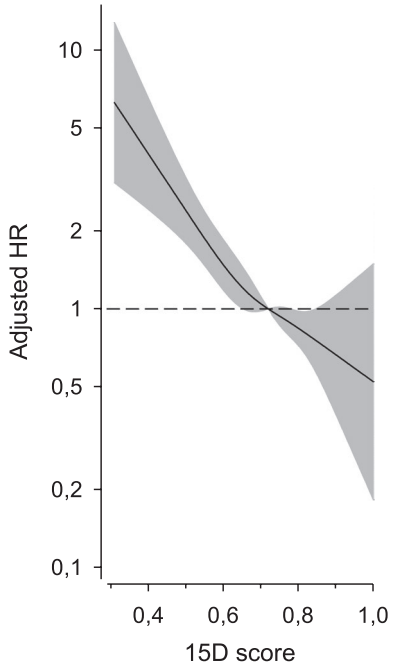

FIGURE 3 The results of the age- and gender-adjusted restricted cubic Sp-lines cox proportional hazards model exploring the non-linear association of the 15D score and the hazard of death. A median of the study population's 15D score (0.717) was set to have a relative HR of 1. As the 15D score decreases, a marked increase in the hazard of death is observed. An increase in the 15D score is not clearly associated with the reduction in the hazard of death

heterogeneous patient group treated in a tertiary pain clinic. All patients admitted for treatment at our tertiary pain clinic were offered a chance to participate, but since reporting reasons for non-participation cannot be required from the patients, this is a source for potential bias. It is possible that there were more patients faring poorly among those who declined to participate.

Since we have data on the survivors only around the time of MPM, not thereafter, comparisons between survivors and the deceased regarding later risk factors for early death were not possible. Particularly, the effect of medical comorbidities on the risk of death or on poor HRQoL could not be modelled. The number of patients is small in some subgroups (e.g. those who committed suicide) despite the large sample size. Further, we do not have population-level data on comorbidities classified with the CACI method and we had no detailed data on opioid use prior to death in the study patients.

4.2 | Implications for future research

Psychological factors, such as stress-prone personality or unfavourable coping styles, have been shown to contribute to mortality from cancer (Chida et al., 2008; Pinquart & Duberstein, 2010) and cardiovascular diseases (Russ et al., 2012). Future studies are needed to determine the putative protective effects of resilience, optimism and other psychological strengths on the mortality of patients in chronic pain, and whether active treatment of psychological distress could decrease the high mortality in pain patients. The role of medical comorbidities in the excess mortality of patients in chronic pain should be assessed with validated classification methods. Most importantly, we should put more effort into helping those patients in chronic pain who not only fail to benefit from the current treatment efforts but also are at risk of premature death.

5 | CONCLUSIONS

The mortality of patients with chronic pain treated at a tertiary multidisciplinary pain clinic was elevated, especially in the youngest patients. Compared with their peers, the youngest deceased patients had more frequently been burdened by psychiatric disorders. Worse HRQoL, impaired functioning and psychosocial symptoms were clearly associated with elevated mortality of chronic pain patients. Psychosocial support and multidisciplinary pain management strategies should be available already early in the disease course in primary health care to prevent serious long-term problems in patients at risk of chronic pain.

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CONFLICTS OF INTEREST

All authors have completed the ICMJE uniform disclosure form. Pekka Vartiainen reports personal fees (lecture fee) from Orion Pharma, outside the submitted work. Eija Kalso reports personal fees (advisory board membership) from Pfizer and Orion Pharma, outside the submitted work. The authors report no other relationships or activities that could appear to have influenced the submitted work. The study sponsors had no part in the study design, and the study was carried out independently from the sponsors.

AUTHOR CONTRIBUTION

TH initiated the current project. All of the authors designed the study, and TH and PV collected the data. PV

designed the statistical analyses with the help of statisticians (acknowledged next). PV and TH were responsible for the writing of the manuscript, and all authors reviewed and revised the manuscript.

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SUPPORTING INFORMATION

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