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Prospective clinical observational study evaluating gender-associated differences of preoperative pain intensity

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Abstract

Previous studies reported conflicting results concerning different pain perceptions of men and women. Recent research found higher pain levels in men after major surgery, contrasted by women after minor procedures. This trial investigates differences in self-reported preoperative pain intensity between genders before surgery.

Patients were enrolled in 2011 and 2012 presenting for preoperative evaluation at the anesthesiological assessment clinic at Charité University hospital. Out of 5102 patients completing a computer-assisted self-assessment, 3042 surgical patients with any preoperative pain were included into this prospective observational clinical study. Preoperative pain intensity (0–100 VAS, visual analog scale) was evaluated integrating psychological cofactors into analysis.

Women reported higher preoperative pain intensity than men with median VAS scores of 30 (25th–75th percentiles: 10–52) versus 21 (10–46) ($P < 0.001$). Adjusted multiple regression analysis showed that female gender remained statistically significantly associated with higher pain intensity ($P < 0.001$). Gender differences were consistent across several subgroups especially with varying patterns in elderly. Women scheduled for minor and moderate surgical procedures showed largest differences in overall pain compared to men.

This large clinical study observed significantly higher preoperative pain intensity in female surgical patients. This gender difference was larger in the elderly potentially contradicting the current hypothesis of a primary sex-hormone derived effect. The observed variability in specific patient subgroups may help to explain heterogeneous findings of previous studies.

Abbreviations: ASA = American Society of Anaesthesiologists physical status classification system, AUDIT = Alcohol Use Disorders Identification Test, BRIA = Bridging Intervention in Anaesthesiology, CCI = Severity of medical comorbidity with the Charlson Comorbidity Index, EQ-5D = European Quality of Life-5 Dimensions, HADS = Hospital Anxiety and Depression Scale, POSSUM = Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity, VAS = visual analog scale for pain.

Keywords: gender, pain, sexes, surgery, vas

Editor: Kazuo Hanaoka.

Funding: this study was supported by the DFG (German Research Foundation, Bonn, Germany; Grant KR 3836/3-1). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Presentation: preliminary data for this study were presented as a poster presentation at the European Society of Anaesthesiology (ESA) Euroanaesthesia, May 30–June 2, 2015, in Berlin.

Trial registration: Clinicaltrials.gov identifier: NCT01357694.

Conflicts of interest: The authors have declared that no competing interests exist regarding this study. Unrelated to this project, ST received lecture fees from Pfizer and Roche and MS from Grünenthal, Develco and Teva. Unrelated to this work, CS received grants from German Federal Ministry of Economics, Grünenthal, Köhler Chemie, Roche, MSD SHARP & DOHME GmbH, Orion Pharma, Outcome Europe Sàrl, B. Braun Melsungen, AppAdventure, Arbeitsgemeinschaft industrieller Forschungsvereinigungen „Otto von Guericke" e. V., Professional Association of German Anaesthesiologists, Federal Ministry of Education and Research, German Cancer Aid, German Aerospace Center, German Research Society, German Society for International Global Health Collaboration, Non-Profit Society Promoting Science and Education, European Commission Funding, European Society of Anaesthesiology; and personal fees from ConvaTec International Service GmbH, Pfizer Pharma, Vifor Pharma, Fresenius Kabi, Georg Thieme Verlag.

The authors have no conflicts of interest to disclose.

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Medicine (2016) 95:27(e4077)

Received: 21 March 2016 / Received in final form: 7 June 2016 / Accepted: 7 June 2016

http://dx.doi.org/10.1097/MD.0000000000004077

1. Introduction

During the last 20 years, gender-related differences came into focus of increasing interest in medical sciences.[1] The observation of significant differences in clinical presentation of diseases like the acute coronary syndrome and divergent response to medical treatment finally led to the recommendation to include women and men equally into clinical trials.[2,3] To date, there are several studies evaluating gender-related differences in the perception of pain intensity.[3] A systematic literature review audited >100 reports of experimental pain trials.[4] In this article, Racine et al found evidence for lower thresholds for pressure pain as well as lower tolerance for thermal (heat and cold) and pressure pain in women.[4] Similar findings were observed using the standardized instrument of quantitative sensory testing that was developed for reliable pain perception measurement and pain thresholds of individuals.[5] From these data, it can be summarized that there is sufficient experimental evidence for specific gender-related differences in pain perception.[6] Furthermore, pain treatment responses may differ between genders.[7] From the pathophysiological point of view, the observed differences were most commonly attributed to differences in hormones.[3] Veldhuijzen et al demonstrated that women show a considerable variability in pain thresholds depending on their current hormone status.[8] Other authors addressed neuronal structures and connectivity as potential sources of gender-related differences in pain.[9,10] For example, Kern et al showed gender-related differences in activation of anterior cingulate and insular regions after painful stimulation in volunteers.[9]

Surprisingly, translation of experimental findings into the clinical setting showed conflicting results. Higher intensity of postoperative pain was observed in female surgical patients in some studies [2,11,12] and in male patients in others [13,14]. In a large-scale trial including >10,000 patients, women had higher postoperative pain levels following minor surgery but men in major surgery.[15] A recent register study from Sweden in lumbar disc herniation surgery described a plain increase of 6 per 100 points visual analog scale for pain (VAS) preoperatively in females.[16] Unfortunately, most studies were limited to postoperative data on gender differences in pain or did not control for additional patient characteristics. Previous clinical trials in surgical patients showed remarkable associations between pain and diverse domains of psychological distress such as anxiety [17,18], depression [19–21], and substance use disorders.[22,23] Thus, gender research on preoperative pain in surgical patients should take into account possible interacting effects of psychological distress.

Taken altogether, there is currently limited data available on gender-related differences in preoperative pain including assessment of psychological distress. Therefore, this study investigates whether male and female surgical patients differ regarding self-reported pre-operative pain intensity after controlling for relevant domains of psychological distress and important somatic parameters.

2. Methods

2.1. Study design and setting

This prospective clinical observational study is part of the research project *Bridging Intervention in Anaesthesiology* (BRIA), which was approved by the Ethics Committee of Charité-Universitätsmedizin Berlin [EA1/014/11] and was conducted according to the principles expressed in the Declaration of Helsinki. The study was registered at ClinicalTrials.gov (NCT01357694). All patients provided written informed consent. The Charité University Hospital is a tertiary care facility in Berlin, Germany. The full details of the setting, assessment instruments, and recent substudies of the BRIA project are available elsewhere [24].

2.2. Patients and data collection

Patients presenting before elective surgery in the preoperative anesthesiological assessment clinics of the Department of Anaesthesiology were invited for study participation. Eligibility criteria were defined as follows. Inclusion criteria were: written informed consent to participate after having been properly instructed; patient of the preoperative anesthesiological assessment clinic; age ≥18 years. Exclusion criteria were: surgery with an emergency or urgent indication (e.g., bone fractures with neurological deficits, nephrolithiasis with colic pain); inability to attend the preoperative assessment clinic (bedside visit); insufficient knowledge of German language; members of the hospital staff; admitted in police custody; accommodation in an institution by official or court order; being under guardianship; psychiatric, neurological or other conditions associated with limited legal capability or limited capability of being properly instructed or giving informed consent.

After obtaining written informed consent, patients were asked to complete a computer-assisted psychosocial self-assessment including validated questionnaires and scoring systems to assess social, lifestyle, and psychological factors as well as pain-related items. Patients were supported by study personnel in case of questions arising during the assessment. For the specific purpose of this analysis, we selected data of those patients who reported any pain or physical discomfort in the EQ-5D questionnaire.[25]

2.3. Definitions and measurement

The preoperative computer-assisted self-assessment included single-item questions concerning diverse sociodemographic and clinical characteristics, as well as a set of standardized screening questionnaires covering the domains of quality of life, well-being, depression, anxiety, alcohol use disorder, and perceived current stress. In this study, we used "European Quality of Life-5 Dimensions" (EQ-5D),[25] "Hospital Anxiety and Depression Scale" (HADS),[26] "Alcohol Use Disorders Identification Test" (AUDIT), [27,28] as well as an adapted version of the "Distress Thermometer" [29] to measure the acute perceived stress level on a scale from 0 to 10 for the domains daily life, current hospital stay, and scheduled surgery. Medical data were obtained from the electronic patient management system of the hospital following surgery. As an overall indicator for the physical health status, we used the evaluation of patients' perioperative risk according to the ASA (American Society of Anaesthesiologists) physical status classification system.[30] This evaluation was performed by the anesthesiologists who did the preoperative assessment. We assessed the severity of medical comorbidity with the Charlson Comorbidity Index (CCI),[31] which is a widely used weighted classification system of comorbidity to measure the cumulative burden of disease in clinical outcome research.[32] According to the coding algorithm of Quan et al,[33] we screened data of the hospital's electronic patient management system for ICD-10 codes indicating the 19 CCI comorbidities. We calculated the CCI taking both major and secondary diagnoses into account. For data analyses, we transformed raw scores to 4 comorbidity

grades according to Charlson et al[31]: (0) "none": 0 points; (1) "low": 1–2 points; (2) "moderate": 3–4 points; (3) high: ≥5 points. Based on the indicated comorbidities, patients were characterized according to concomitant diagnoses of congestive heart failure, periphery arterial obstructive disease, cerebrovascular diseases, chronic pulmonary disease, rheumatic diseases, chronic liver disease, diabetes mellitus, chronic renal disease or malignoma. To quantify the severity of scheduled surgical procedures, we applied the 4-point item "operative severity" of the POSSUM scoring system (Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity).[33] Based on previously published classification schemes, we assigned the specific surgical procedures to 1 of the 4 severity grades (minor = 1; moderate = 2; major = 4; major+ = 8). For this classification, we used the standardized German codes of surgical procedures.[34] Details on psychological and medical measures can also be found in recent descriptions of the BRIA project.[24,35]

2.4. End points

The visual analog scale (VAS) for self-reported preoperative pain intensity was measured as the primary study parameter. Patients were asked to rate their current pain intensity on a scale ranging from 0 to 100 points. As secondary end points of this study, subgroup analyses were performed to explore patterns of pain intensity in the cohort. For this purpose, age decades, clinically relevant depression and anxiety, as well as severity of surgical procedure were used as covariates.

2.5. Statistical analysis

Results are presented depending on their scale level as relative frequencies in percent, median, and range of the 25th–75th percentiles. All analyses for statistical significance were performed 2-sided with an alpha of <5% as the significance level. For univariate analyses of significance, the Wilcoxon–Mann–Whitney test or Fisher's exact test was used as appropriate. Due to inclusion of skewed distributed dependent variables and ordinal covariates, linear regression was not an appropriate analysis. For this purpose, the technique of robust regression analyses was applied.[36] In the robust regression model, VAS of pre-operative pain intensity was the dependent variable, and relevant basic characteristics that differed between genders were included as covariates: age, status of employment, living with partner, comedications, clinically relevant depression, clinically relevant anxiety, perceived stress level, alcohol-related problems, and use of illicit drugs. Additionally, ASA classification, overall Charlson Comorbidity Index, and specific comorbidities like history of diabetes mellitus, renal or malignant diseases in medical history and the admitting specialty were included into the regression model, along with BMI and classified severity of operation. The variables were processed in a backward elimination procedure. The resulting coefficients including 95% bootstrap confidence intervals are displayed for the last step of the analysis. All analyses were performed with IBM SPSS 22.0 or R 3.0.2.

3. Results

From May 2011 to June 2012, 13,751 patients were assessed for eligibility. Altogether 5102 patients completed the preoperative computer-assisted self-assessment. Based on the included EQ-5D evaluation, 991 women and 1069 men reported currently not having any pain or physical discomfort. Finally, a total of 1487 female and 1555 male patients fulfilled inclusion criteria for this

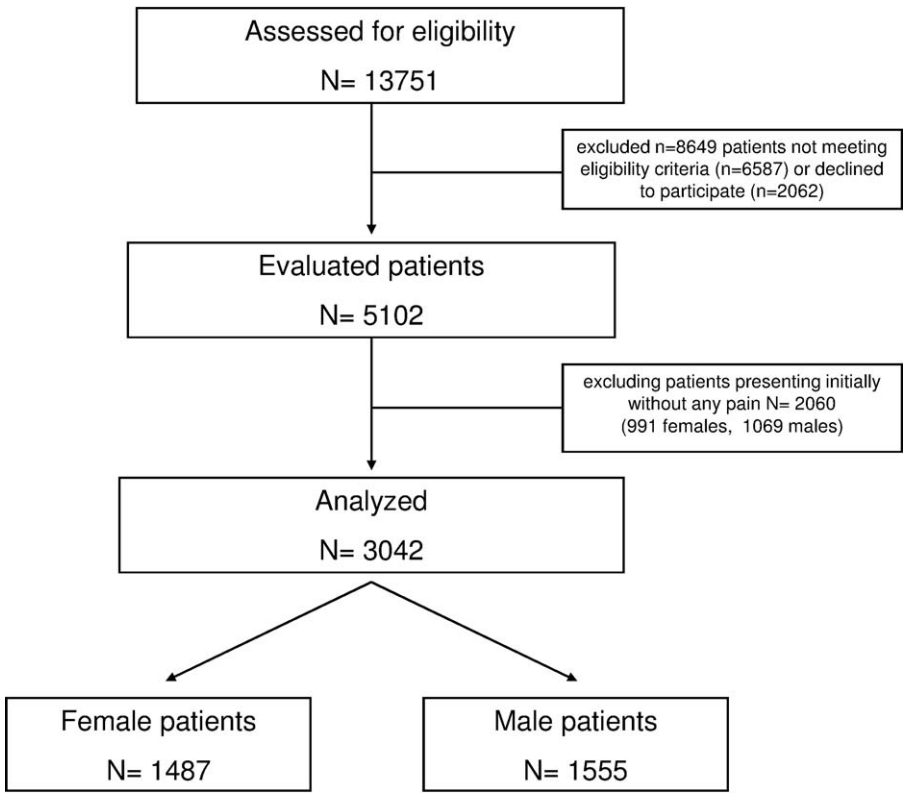

Figure 1. Study flowchart.

Table 1

Demographic and clinical characteristics of included female and male patients (N = 3042); n (%), median [25th–75th percentiles].

Variables	All patients N = 3042	Women N = 1487 (48.9%)	Men N = 1555 (51.1%)	*P*
Age (y)	49 [37–60]	47 [36–57]	51 [38–62]	<0.001
Employment status				0.029
Employed, in education/training	1825 (60.0)	922 (62.0)	903 (58.1)	
Unemployment, in pension, others*	1217 (40.0)	565 (38.0)	652 (41.9)	
Living with partner	1870 (61.5)	858 (57.7)	1012 (65.1)	<0.001
Comedication				
Pain medication	985 (32.4)	541 (36.4)	444 (28.6)	<0.001
Sleep-inducers	130 (4.3)	76 (5.1)	54 (3.5)	0.031
Tranquilizer	91 (3.0)	56 (3.8)	35 (2.3)	0.014
Antidepressants	208 (6.8)	129 (8.7)	79 (5.1)	<0.001
Other psychiatric medication	100 (3.3)	44 (3.0)	56 (3.6)	0.360
Depression and anxiety				
Clinically relevant depression†	586 (19.3)	319 (21.5)	267 (17.2)	0.003
Clinically relevant anxiety†	526 (17.3)	354 (23.8)	172 (11.1)	<0.001
Perceived stress level (0–10)				
Daily life	5 [2–7]	5 [3–8]	4 [2–6]	<0.001
Current hospital stay	4 [2–7]	5 [2–8]	3 [2–6]	<0.001
Upcoming surgery	5 [2–8]	5 [3–8]	4 [2–7]	<0.001
Substance use problems				
Tobacco smoking	1023 (33.6)	487 (32.8)	536 (34.5)	0.319
Alcohol-related problems‡	473 (15.5)	223 (15.0)	250 (16.1)	0.423
Use of illicit drugs	240 (7.9)	80 (5.4)	160 (10.3)	<0.001

* Patients were classified according their self-reported employment status into 2 groups: (1) employed or undergoing education/training (e.g., school, professional training, university); (2) unemployed, pension/invalidity pension, residual group (working at home, gap year, parental leave, not specified).

† Clinically relevant depression according to HADS-D cut-off ≥9; clinically relevant anxiety according to HADS-A cut-off ≥11 (Hospital Anxiety and Depression Scale).

‡ Alcohol-related problems according to AUDIT cut-off ≥5 for women and ≥ 8 for men (Alcohol Use Disorders Identification Test).

analysis and consequently comprised the study population (Fig. 1).

Demographic and clinical basic characteristics differed statistically significantly between genders (Table 1). Women were younger, slightly less likely to live with a partner and more likely to be employed or undergoing education. They had higher rates of clinically relevant depression and anxiety, and a lower rate of illicit drug use. Additionally, they showed higher levels of perceived stress concerning daily life, the hospital stay, and the scheduled surgery and were more likely to use pain medications, sleep-inducers, tranquilizers, and antidepressants (Table 1).

Regarding medical characteristics, women showed statistically significantly better overall preoperative physical health status according to the ASA classification and less medical comorbidity according to the Charlson Comorbidity Index and in terms of less comorbidities (Table 2). In contrast, a higher proportion of female patients underwent subsequent major surgery.

3.1. Assessment of preoperative Pain

Current pain intensity differed statistically significantly between women and men with female patients reporting a median VAS of 30 (10–52 IQR) and male patients a median VAS of 21 (10–46 IQR), $P < 0.001$.

3.2. Multivariate validation

To account for the observed differences of female and male patients regarding basic characteristics, we conducted a robust regression analysis including relevant potential confounding variables. In this multiple regression model, female gender was found to remain statistically significantly and independently associated with increased pain intensity before surgery with a regression coefficient of 1.673 (95% CI 0.538–2.858, Table 3).

3.3. Subgroups

The large sample size allowed further subgroup analyses. Most interestingly, there was a very large variability in pain intensity scores depending on age categories as shown in Fig. 2. In patients between 18 and 39 years, pain intensity differences between men and women did not reach statistical significance ($P > 0.05$, Fig. 2).

However, in patients at the age of 40 years and older, differences were statistically significant and increased considerably in older age groups with the largest difference observed in patients >75 years.

Clinically relevant anxiety and depression were associated with preoperative pain intensity in both, men and women. Here, patients with clinically relevant anxiety or depression showed higher preoperative VAS values (Fig. 3).

Additionally, women showed consistently higher median pain intensities compared to men in patients with and without clinically relevant anxiety or depression ($P < 0.05$ for both analyses). Pain intensity showed also relevant variability depending on severity of subsequent surgical procedure. In patients with major or very large surgical procedures, VAS scores were higher, and differences between men and women were not statistically significant. However, in minor and moderate surgical procedures, women reported significantly higher preoperative VAS as compared to men ($P < 0.05$; Fig. 4).

4. Discussion

The most important finding of this study is that preoperative pain intensity differed significantly between female and male surgical patients. The magnitude of plain difference in preoperative pain intensity between genders achieved 9/100 VAS points. Most interestingly, although women presented with higher preoperative pain intensity, specific subgroups showed relevant variability

Table 2

Medical characteristics of included patients (N = 3042) and comparison of women and men; n (%), median (25th–75th percentiles).

Variables	All patients N = 3042	Women N = 1487 (48.9%)	Men N = 1555 (51.1%)	P
Physical health (ASA classification)*				
ASA I	686 (22.6)	316 (21.3)	370 (23.8)	<0.001
ASA II	1868 (61.4)	965 (64.9)	903 (58.1)	
ASA III	474 (15.6)	202 (13.6)	272 (17.5)	
ASA IV	14 (0.5)	4 (0.3)	10 (0.6)	
Body mass index	25.8 [23.0–29.4]	25.2 [22.0–29.3]	26.3 [23.9–29.4]	<0.001
Medical comorbidity (CCI)†				
0 "None"	2109 (69.3)	1098 (73.8)	1011 (65.0)	
1 "Low"	590 (19.4)	252 (16.9)	338 (21.7)	<0.001
2 "Moderate"	168 (5.5)	53 (3.6)	115 (7.4)	
3 "High"	175 (5.8)	84 (5.6)	91 (5.9)	
Comorbidities				
Congestive heart failure	38 (1.2)	14 (0.9)	24 (1.5)	0.145
Periphery arterial obstructive disease	83 (2.7)	33 (2.2)	50 (3.2)	0.096
Cerebro-vascular diseases	26 (0.9)	12 (0.8)	14 (0.9)	0.845
Chronic pulmonary disease	161 (5.3)	74 (5.0)	87 (5.6)	0.467
Rheumatic disease	25 (0.8)	17 (1.1)	8 (0.5)	0.070
Chronic liver disease	66 (2.2)	28 (1.9)	38 (2.4)	0.320
Diabetes mellitus	244 (8.0)	89 (6.0)	155 (10)	<0.001
Chronic renal disease	95 (3.1)	32 (2.2)	63 (4.1)	0.003
Malignoma	467 (15.4)	181 (12.2)	286 (18.4)	<0.001
Location of operation				
General surgery	261 (8.6)	116 (7.8)	145 (9.3)	
Trauma	588 (19.3)	231 (15.5)	357 (23.0)	<0.001
Neurosurgery	126 (4.1)	53 (3.6)	73 (4.7)	
Urology and gynaecology	634 (20.8)	414 (27.8)	220 (14.1)	
Orthopaedic surgery	689 (22.6)	325 (21.9)	364 (23.4)	
Extracranial surgery (ear nose throat)	359 (11.8)	178 (12.0)	181 (11.6)	
Extracranial surgery (eyes)	104 (3.4)	53 (3.6)	51 (3.3)	
Extracranial surgery (maxillofacial)	131 (4.3)	57 (3.8)	74 (4.8)	
Dermatology	59 (1.9)	19 (1.3)	40 (2.6)	
miscellaneous	91 (3.0)	41 (2.8)	50 (3.2)	
Severity of scheduled surgery‡				
"1" minor	1189 (39.1)	559 (37.6)	630 (40.5)	
"2" moderate	799 (26.3)	375 (25.2)	424 (27.3)	0.026
"4" major	744 (24.5)	395 (26.6)	349 (22.4)	
"8" major+	235 (7.7)	114 (7.7)	121 (7.8)	
No surgery	75 (2.5)	44 (3.0)	31 (2.0)	

* ASA classification (American Society of Anesthesiologists). ASA I, II: healthy patients (ASA I) and patients with mild systemic disease, no functional limitations (ASA II); ASA III, IV: patients with severe systemic disease with definite functional limitation (ASA III) and patients with severe systemic disease that is a constant threat to life (ASA IV).

† CCI (Charlson Comorbidity Index).

‡ POSSUM operative severity item (Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity), including patients without consecutive operation during the hospital stay (females N = 44, males N = 31).

especially depending on age categories and severity of subsequent surgical procedures.

However, female and male patients also varied in distribution of baseline characteristics, a finding that has been anticipated based on results from previous studies.[17,37,38] To account for this heterogeneity, robust regression analysis was performed to evaluate the independent effect of gender. In this multiple regression model, the factor of female gender remained significantly associated with higher VAS scores. Along with our findings, a recent register-study showed an increased preoperative pain intensity in females scheduled for spine surgery.[16] Similarly, most parameters of physical and mental health differed between genders in this Swedish population. In concordance with these preoperative data, female gender has been described to be associated with elevated postoperative pain intensity in different settings. In a study investigating patients following coronary artery bypass graft surgery, Totonchi et al found higher pain intensity in women on day 7 postoperatively.[11] In these patients, age correlated negatively with pain intensity and 1 highly relevant and potentially modifiable factor for increased postoperative pain was the persistence of the chest tube. Stromqvist et al studied patients following surgery for spinal disc herniation and demonstrated an increased pain intensity of a mean of 11 VAS points for female patients.[12] Notably, the authors followed the study cohort for 1 year and women still required significantly more often analgesics at this time point. Sufficient control of perioperative pain has especially been addressed with the intention to prevent patients from developing chronic pain.[39] In long-term follow-up, intensity of pain remained significantly different between genders as shown for neuropathic postoperative pain [40] and for patients with phantom pain.[14] Additionally, psychological assessment showed more pronounced catastrophing in women but also higher presence of coping strategies for pain.[14]

In the literature, the influence of concomitant depression on pain intensity has already been described [19] and psychological distress contributed significantly to variability of VAS also in this study. A higher incidence of chronic pain has been described for

Table 3

Multiple regression analysis of demographic and clinical characteristics associated with preoperative intensity of pain (VAS, 0–100); results of the last step of the resulting backward selection model with the specific regression coefficients and 95% confidence intervals (N = 3042).

Variables	Coefficient	95% Confidence interval		*P*
		Lower CI	Upper CI	
Female gender	1.673	0.538	2.858	0.004
Age	0.073	0.036	0.11	0.001
Employed or in education/training*	1.838	0.545	3.116	0.004
Living with partner	0.512	–0.792	1.38	0.378
No use of pain medication	–29.279	–37.335	–24.114	<0.001
No use of sleep-inducers	–2.087	–6.747	3.443	0.217
No use of tranquilizers	–2.587	–6.722	4.89	0.179
No use of antidepressants	–3.538	–6.164	–0.207	0.006
Clinically relevant depression†	5.474	2.947	7.363	<0.001
Clinically relevant anxiety†	0.694	–0.888	2.818	0.443
Stress level concerning daily life	0.552	0.353	0.728	<0.001
Alcohol-related problems‡	–1.251	–2.751	0.068	0.099
Physical health (ASA classification)§				
I	*reference category*			
II	1.76	0.625	2.979	0.01
III	3.988	1.709	5.892	<0.001
IV	4.547	–2.697	10.75	0.262
Medical comorbidity (CCI)‖				
None	*reference category*			
Low	2.387	0.154	4.365	0.018
Moderate	0.44	–2.664	2.59	0.778
High	1.219	–2.226	4.986	0.492
Diabetes mellitus in medical history	–1.704	–3.699	0.794	0.161
Malignoma in medical history	–3.927	–6.351	–1.511	0.001
Admitting surgical speciality				
General surgery	*reference category*			
Trauma	8.316	5.495	11.11	<0.001
Neurosurgery	2.07	–2.166	7.826	0.234
Urology or Gynecology	–1.923	–3.457	–0.069	0.068
Orthopedics	15.657	12.1	20.281	<0.001
Extracranial surgery (ear nose throat)	–1.6	–3.585	0.579	0.183
Extracranial surgery (eyes)	–0.951	–2.805	1.517	0.549
Extracranial surgery (maxillofacial surgery)	–0.89	–3.153	2.33	0.559
Dermatology	–0.396	–2.993	2.606	0.833
Miscellaneous	–2.577	–4.487	0.106	0.117
Severity of scheduled surgery¶				
Minor	*reference category*			
Moderate	–0.865	–2.3	0.609	0.24
Major	1.588	0.003	3.488	0.035
Major plus	1.915	–0.564	5.181	0.106
No operation or operation cancelled	1.915	–0.564	5.181	0.106
Body mass index	0.234	0.102	0.35	<0.001

Included into the model: age, employment status, living with partner, use of pain medication, tranquilizers, antidepressants or sleep-inducing drugs; clinically relevant depression, clinically relevant anxiety, stress level, alcohol-related problems, smoking, illicit drug abuse, physical health (ASA classification), comorbidity (Charlson Comorbidity group), malignoma, admitting surgical speciality, severity of operation, body mass index.

* Patients were classified according their self-reported employment status into 2 groups: (1) employed or undergoing education/training (e.g., school, professional training, university); (2) unemployed, pension/invalidity pension, residual group (working at home, gap year, parental leave, not specified).

† Clinically relevant depression according to HADS-D cut-off ≥9; clinically relevant anxiety according to HADS-A cut-off ≥11 (Hospital Anxiety and Depression Scale).

‡ Alcohol-related problems according to AUDIT cut-off ≥5 for women and ≥ 8 for men (Alcohol Use Disorders Identification Test).

§ ASA classification (American Society of Anesthesiologists). ASA I, II: healthy patients (ASA I) and patients with mild systemic disease, no functional limitations (ASA II); ASA III, IV: patients with severe systemic disease with definite functional limitation (ASA III) and patients with severe systemic disease that is a constant threat to life (ASA IV).

‖ CCI (Charlson Comorbidity Index).

¶ POSSUM operative severity item (Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity), including patients without consecutive operation during the hospital stay (females N = 44, males N = 31).

women [38,41] although some specific pain syndromes such as cluster headache or post-zoster-neuralgia were found to be associated with male gender.[42] Additionally, gender has been recognized as a significant cofactor influencing response to pain in chronic pain patients. For example, Pieh et al evaluated therapy success of an intensive multimodal pain therapy program. In this trial, women improved more in overall pain intensity compared with men and also showed a higher benefit regarding pain-related disabilities in daily life.[38]

Surprisingly, in our data age subgroups showed a high variability of gender-related pain differences with older age categories showing the highest differences. Indeed, this could

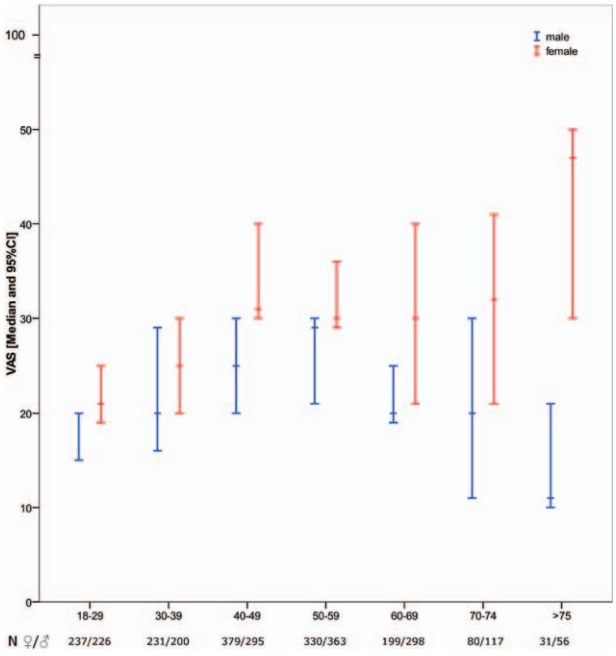

Figure 2. Preoperative intensity of pain (VAS) in female and male patients. Patients are grouped according to age decades, VAS values given as median with 95% confidence intervals (95%CI), including numbers of females/males in each category. Differences between men and women achieved a statistical significance level $P < 0.05$ in age decades ≥40 years. CI = confidence interval, VAS = visual analog scale for pain.

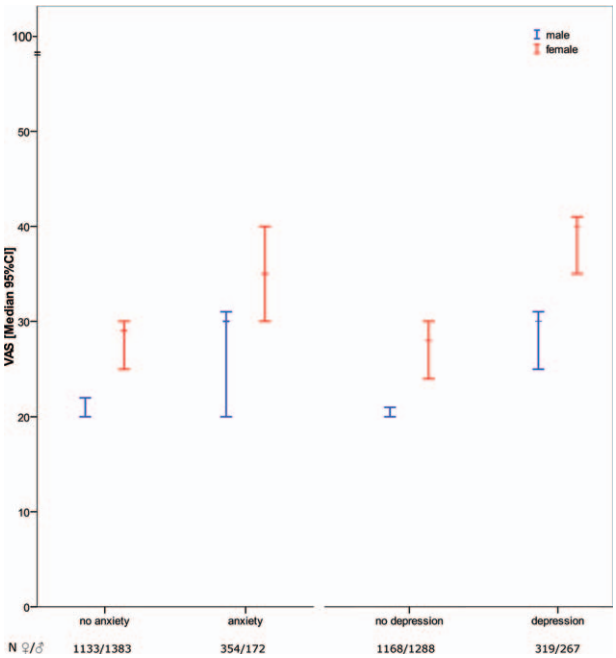

Figure 3. Preoperative intensity of pain (VAS) in female and male patients. Patients are grouped according to HADS evaluation for clinically relevant depression and anxiety, VAS values given as median with 95% confidence intervals (95%CI), including numbers of females/males in each category. Differences between men and women achieved a statistical significance level in all groups ($P < 0.05$). CI = confidence interval, HADS = Hospital Anxiety and Depression Scale, VAS = visual analog scale for pain.

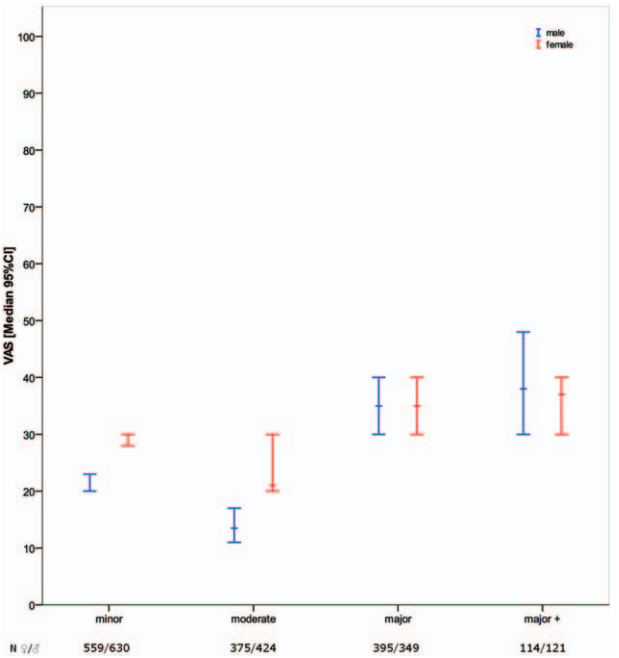

Figure 4. Preoperative intensity of pain (VAS) in female and male patients. Patients are grouped according to severity of subsequent surgery (POSSUM operative severity item), VAS values given as median with 95% confidence intervals (95%CI), including numbers of females/males in each category. Differences between men and women achieved a statistical significance level in minor and moderate categories ($P < 0.05$). CI = confidence interval, POSSUM = Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity, VAS = visual analog scale for pain.

contradict the pathophysiological hypothesis that sex hormones are the primary cause for observed higher pain intensity in female patients.[8] Neuronal structures and connectivity, as well as psychosocial factors, may be of specific importance,[9,10,43] but there is currently no conclusive evidence available to explain the observed variability. Sufficient data of clinical trials evaluating pain intensity and their association with sex hormone levels are not available. Similarly, severity of surgical procedure seems to be a relevant factor. One recent large study suggested different patterns of postoperative pain intensity depending on the surgical procedure performed and found men experiencing more pain after major surgery.[15] In contrast, women reported higher pain intensity following minor surgery. In fact, this difference was also observable in our data as higher preoperatively observed VAS scores were reported by women scheduled for minor and moderate surgery. It seems suggestive that underlying diseases and comorbidities may play an important role to explain these observed gender-related differences. Gender appears to be a cofactor influencing pain intensity in patients undergoing surgery. The background of observed large variability between male and female patients in preoperatively observed pain intensity is currently not well understood and might be especially of interest to tailor gender-specific perioperative interventions.

5. Limitations

Although this study included a large sample of patients from diverse surgical fields who presented for preoperative anesthesiological assessment, the setting is limited to the university hospital and also additional data on postoperative pain were not

available. However, comparable data on preoperative pain intensity have rarely been reported in the literature. The visual analog scale for pain remains the best available tool to measure patients' self-reported pain intensity but also incorporates cognitive influences. Finally, because this study was not a randomized controlled trial, we cannot infer on underlying causalities. Therefore, we carefully explored a large number of cofactors to control for potential confounders and used a powerful statistical method. However, higher degrees of interactions between preoperatively measured pain intensity and clinically relevant anxiety and depression, as well as age or co-medication might, among others, have contributed to the observed gender differences but are currently not statistically assessable. In this study, patients were attributed to female or male gender according to the information from their medical electronic patient data files. Consequently, the term gender was used in this manuscript to account for this self-assigned status of the patients incorporating more than a binary biological status. However, the concept of gender would also include a psychosocial concept of masculinity and femininity, but further exploration of this aspect was not possible due to limitations of the data.

6. Conclusion

Finally, during preoperative pain assessment gender should be considered as 1 key factor that has impact on the preoperative patient's pain intensity; the latter is known to influence postoperative outcome. Therefore, this may help in the decision process of anesthesiologists planning perioperative therapeutic measures for pain control in the individual patient.[44,45]

Gender remains a significant cofactor influencing pain intensity in patients undergoing surgery. The background of observed large variability between male and female patients in preoperatively observed pain intensity is currently not well understood and might be especially of interest to tailor gender-specific interventions.

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