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 anaesthesiological 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
1. Introduction

During the last 20 years, gender-related differences came into focus of increasing interest in medical sciences. 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. To date, there are several studies evaluating gender-related differences in the perception of pain intensity. A systematic literature review audited >100 reports of experimental pain trials. 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. 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. From this data, it can be summarized that there is sufficient experimental evidence for specific gender-related differences in pain perception. Furthermore, pain treatment responses may differ between genders. From the pathophysiological point of view, the observed differences were most commonly attributed to differences in hormones. Veldhuizen et al demonstrated that women show a considerable variability in pain thresholds depending on their current hormone status. Other authors addressed neuronal structures and connectivity as potential sources of gender-related differences in pain. For example, Kern et al showed gender-related differences in activation of anterior cingulate and insular regions after painful stimulation in volunteers.

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 and in male patients in others. In a large-scale trial including >10,000 patients, women had higher postoperative pain levels following minor surgery but men in major surgery. 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. 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, depression, alcohol use disorder, and perceived current stress. In this study, we used “European Quality of Life-5 Dimensions” (EQ-5D), “Hospital Anxiety and Depression Scale” (HADS), “Alcohol Use Disorders Identification Test” (AUDIT), as well as an adapted version of the “Distress Thermometer” 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.

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.

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.

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), “Hospital Anxiety and Depression Scale” (HADS), “Alcohol Use Disorders Identification Test” (AUDIT), as well as an adapted version of the “Distress Thermometer” 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. 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), which is a widely used weighted classification system of comorbidity to measure the cumulative burden of disease in clinical outcome research. According to the coding algorithm of Quan et al, 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...
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 <.05 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.[16] 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, comorbidities, 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 study.

Figure 1. Study flowchart.
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 perceived stress levels and showed higher levels of pain medication use compared to men (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 values 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 pain 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.
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. 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. 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. 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. Notably, the authors followed the study cohort for 1 year and women still required significantly more often analgesics at this point. Sufficient control of perioperative pain has especially been addressed with the intention to prevent patients from developing chronic pain. In long-term follow-up, intensity of pain remained significantly different between genders as shown and psychological distress contributed significantly to variability of VAS also in this study. A higher incidence of chronic pain has been described for

### Table 2

| 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 |
| Periphereal 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 |
| Maligoma | 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 | 598 (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 surgery³ | | | | |
| “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) | |

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* 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).

³ 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).
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 | Lower CI | Upper CI | P       |
|-----------|-------------|----------|----------|---------|
| 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 | 0.005 |
| 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)¶ | reference category | | | |
| I | 1.76 | 0.625 | 2.979 | 0.01 |
| II | 3.088 | 1.709 | 5.892 | <0.001 |
| IV | 4.547 | −2.697 | 10.75 | 0.262 |
| Medical comorbidity (CCI)* | reference category | | | |
| None | 2.387 | 0.154 | 4.635 | 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 specialty | | | | |
| 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 | 0.853 |
| Miscellaneous | −2.577 | −4.487 | 0.106 | 0.117 |
| Severity of scheduled surgery* | reference category | | | |
| Minor | −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 Index), malignoma, admitting surgical specialty, 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 ≥5; 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).

§ Medical comorbidity (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 that is a constant threat to life (ASA IV).

¶ POSSUM operative severity item (Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity). Patients were classified according to 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).

Women [38,41] although some specific pain syndromes such as cluster headache or post-zoster-neuralgia were found to be associated with male gender. Additionally, gender has been recognized as a significant cofactor influencing response to pain in chronic pain patients. For example, Pich 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. [18] 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...
contradict the pathophysiological hypothesis that sex hormones are the primary cause for observed higher pain intensity in female patients. Neuronal structures and connectivity, as well as psychosocial factors, may be of specific importance, 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. 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 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.\textsuperscript{4,45}

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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