

# The impact of pain and bodyweight on the time in post-anesthesia recovery in adult patients : a retrospective cross-sectional study

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**UNIVERSITY OF SPLIT  
SCHOOL OF MEDICINE**

**Philipp Groetsch**

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SECTIONAL STUDY**

**Diploma thesis**

**Academic year:**

**2021/2022**

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**Assist. Prof. Georg Breuer, MD, PhD**

**Split, August 2022**

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## LIST OF ABBREVIATIONS

|        |   |  |
|--------|---|--|
| 5-HT   | – | 5-hydroxytryptamine (Serotonin)                              |
| ACC    | – | Anterior cingulate cortex                                    |
| AMPA   | – | $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid |
| AP     | – | Action potential   |
| ASA    | – | American Society of Anesthesiologists                        |
| ASIC   | – | Acid-sensing ion channel                                     |
| ATP    | – | Adenosine triphosphate                                       |
| BMI    | – | Body Mass Index  |
| BCE    | – | Before Common Era  |
| CE     | – | Common Era   |
| CGRP   | – | Calcitonin gene-related peptide                              |
| CHIPPS | – | Children's and Infants' Postoperative Pain Scale             |
| CNS    | – | Central nervous system                                       |
| COX    | – | Cyclooxygenase   |
| DRG    | – | Dorsal root ganglion   |
| ECG    | – | Electrocardiogram  |
| FNE    | – | Free nerve ending  |
| FPS-R  | – | Faces Pain Scale revised                                     |
| GABA   | – | $\gamma$ -Aminobutyric acid                                  |
| GCT    | – | Gate control theory  |
| IASP   | – | The International Association on the Study of Pain           |
| ICU    | – | Intensive care unit  |
| LOS    | – | Length of stay   |
| mRNA   | – | Messenger ribonucleic acid                                   |
| NMDA   | – | N-methyl-D-aspartate   |
| NRS    | – | Numerical Rating Scale                                       |
| NSAID  | – | Non-steroidal anti-inflammatory drugs                        |
| OR     | – | Operating room   |
| PACU   | – | Post-anesthesia care unit                                    |
| PAG    | – | Periaqueductal gray  |
| PAN    | – | Primary afferent nociceptor                                  |

|      |   |  |
|------|---|--|
| pH   | – | Power of hydrogen                            |
| PNS  | – | Peripheral nervous system                    |
| PONV | – | Postoperative nausea and vomiting            |
| PVG  | – | Periventricular gray                         |
| RF   | – | Receptive field                              |
| SNRI | – | Serotonin-norepinephrine reuptake inhibitors |
| STT  | – | Spinothalamic tract                          |
| TG   | – | Trigeminal ganglion                          |
| TIVA | – | Total intravenous anesthesia                 |
| TRP  | – | Transient receptor potential                 |
| VAS  | – | Visual Analogue Scale                        |
| VRS  | – | Verbal Rating Scale                          |
| VPL  | – | Ventral posterolateral nucleus               |
| VPN  | – | Ventral posterior nucleus                    |
| WDR  | – | Wide dynamic range neurons                   |

## **1. INTRODUCTION**



## 1.1. Pain

The Sumerian clay tablet, believed to be the first documented medical prescription, dates back to 2100 BCE, from an ancient Mesopotamian civilization (1). Historical research believes that there is evidence that the tablet refers to the use of opium poppy as a painkiller (1). Later, Pedanius Dioscorides, a first-century Greek physician, and independently, the Roman encyclopedist Celsus, in his work *De Medicina* (~47 CE), both proposed the use of opium in combinations prior to a surgery (1, 2).

A universal physical condition, which has existed throughout the history of mankind as the oldest medical problem (3), will yet take another eighteen centuries since Celsus to be partially overcome with the predecessor of modern anesthesia (i.e., ether overcame surgical pain) (4), and was only finally defined less than forty years ago (5). And even up to the present time, experts are constantly refining how to fully and comprehensively describe this field of medicine due to the ongoing fruitful scientific advancements (6).

In short terms, the concept of “pain” combines two mutually supplementary aspects: the local perception at the site of the event and a hurtful experience of varying intensity, which is usually accompanied by behavioral changes aimed at reducing or stopping the occurrence and recurrence of the event (7). According to our current knowledge, free nerve endings (FNE) on the peripheral side of pseudounipolar neurons (8), having their soma in the dorsal root ganglions (DRGs), respond to (potentially) harmful stimuli. They send already modified messages over specific well-identified nerves (A- and C-fibers) in the peripheral nervous system (PNS), the so-called primary afferent nociceptors (PAN) (Latin *nocere* “to harm”), to the central nervous system (CNS) (7–9). These peripheral nerves (i.e., first order neurons) will junction with their central processes in the dorsal horn of the spinal cord to second-order neurons that ascendingly relay the stimuli to higher centers, most notably the thalamus and cortex (7, 10). These, together with other cortical plastic neurons, make up the pain neuromatrix, which itself is determined by genetics as well as influenced by learned physical sensation (7, 11).

From an evolutionary point of view, pain has the physiological function of an alarm system that alerts to possible and actual injury to tissue (12). Pain is a fundamental component of the human experience, making it one of the few constants in humanity and between its innumerable cultures (13). Its design has also proven to be sufficiently effective, seen in that it has most similarly been carried over and advanced across species with the usual evolutionary necessary adaptations. Newer research approaches to further uncover this only partly understood topic now successfully include crustaceans and other invertebrate species (12, 14, 15). These results may change our perspective once again in the future.

### **1.1.1. Definition of pain**

Leading global experts in this field, united within The International Association on the Study of Pain (IASP), elaborated their following definition, which is widely accepted by researches, non-governmental, and state organizations, including the European Pain Federation EFIC (5, 6, 16). It currently states: “An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage” (5, 6).

The authors have provided the following additional elements to the definition for clarification, underscoring the topic's complexity. They note that pain is always a subjective sensation impacted by organic, psychological, and social elements (17) to various degrees. Perceived pain and noxious stimuli are two separate events, which are mutually dependent on each other. Pain cannot be deduced merely from sensory neural responses alone. Further, individuals learn about suffering throughout their experiences and knowledge. Every person's complaint of pain must be taken seriously. While pain is normally adaptive, it can have a permanent negative impact on performance as well as psychological and emotional health. And lastly, verbal description is just one of multiple ways to express agony; the inability to verbalize does not rule out the that a person or any other species is suffering (6).

### **1.1.2. Classification of pain**

Pain is classified by different characteristic features, given it has a multidimensional nature (18, 19). First, probably the most commonly used division is made based upon duration. Pain that is recent or will last for a foreseeable time is called acute pain. It is usually possible to attribute it to a specific cause such as intense mechanical stimulation, i.e., surgical incision (20). It is the closest pain type to be evolutionarily conserved and has a key role as a defensive mechanism (21). Since this "direct" form is the natural consequence of a surgical intervention, meaning the perioperative pain (22, 23), it will be the main component of this thesis.

Given the duration is persistent or recurring for longer than 3 months, it is called chronic pain (24, 25). It may be the protracted consequence of postoperative pain or arise from its own pathologies, and thus, has little use in evolutionarily context (26). It is a major challenge for most pain patients, as it can be associated with disabilities such as sleep deprivation, fatigue, or social setbacks (27). All these sequels then in turn have consequences of their own, which makes this clinical entity very complex and difficult to target (27). To prevent chronicity, established mainly by peripheral or central sensitization, measures like regional anesthetic and pre-emptive analgesia proved essential in the management of acute perioperative pain (28). It is also noteworthy that literature seems to have difficulty fitting (chronic) malignant cancer-

related pain into this category, which means that it is often referred to as a separate entity alongside acute and chronic pain (29).

Another comprehensive etiology-based approach (i.e., causes and origins of diseases), proposed by Bonezzi et al., relates neuropathic pain to a direct dysfunction of neurons in the CNS and PNS. Leading to either local or general symptoms, it is thought to be mainly elicited by ectopic impulses (30). These ectopic loci are typically to be found on injury sites along the PAN or in the DRGs, meaning they are mimicking stimuli from FNE (31). Neuropathic pain is a prevalent condition whose etiology, in turn, varies widely (32), some prominent examples being peripheral neuropathic pain, lesions in the CNS or HIV-associated neuropathy (30).

The more common biological mechanism is nociceptive pain, responsible for the detection and transmission of high-threshold noxious stimuli (heat, mechanical or chemical injury) in non-neural somatic and visceral tissues (23, 30). Since some of the receptors (e.g., acid-sensing ion channels (ASICs) and transient receptor potential (TRP) cation channel family) on associated fiber ends seem to be able to detect inflammation (33, 34), “inflammatory pain” is sometimes used synonymously or in close relation with the nociceptive pain class. The same mechanism and receptors can sense general ischemia or cardiac pain, happening in myocardial ischemia or infarction, as well (23, 35). Nociceptive and neuropathic pain have in common, among other properties, that they are involved in the conditioning of allodynia and hyperalgesia. Two common clinical features in which indiscriminate pain is felt due to a stimulus that would normally not elicit pain at all and exaggerated pain due to a stimulus that usually would provoke minor pain, respectively (23, 36).

The third and most recently accepted class is nociplastic pain. A change in the perception of pain in the absence of actual or impending tissue damage and in the absence of nervous system injury or pathology is associated with central sensitization and with psychological distress (30). It is postulated that hypersensitization of nociceptive pain may act as a precursor to nociplastic pain (30, 37). Well-known examples are fibromyalgia syndrome or chronic non-specific low back pain (30).

“Mixed pain” is a compound overlapping of the abovementioned pain classes (nociceptive, neuropathic, nociplastic) in any combination, simultaneously causing pain in the same body part and either mechanism may be dominating clinically at various times, a fairly new and loosely defined notion (38).

### **1.1.3. Anatomy of pain**

#### **1.1.3.1. Pain and the nociceptive system**

Before describing the anatomical basis, one must fully grasp the difference between pain and nociception. The latter constituting the process of neural encoding and transmission of signals generated on activation of peripheral neurons within or on the surface of the body by impending or actual organic matter damage, i.e. a noxious stimuli (e.g. heat, hypoxia, chemical injury including chemotherapeutic drugs) (8, 39). Whereas the subjective experience (i.e., emotion) of pain is the product of higher brain functions, in the thalamocortical processing centers (7, 10, 39, 40). Bearing in mind that this system does not have the same high sensitivity as the auditory organ (8), the described distinction is probably best compared to our perception of speech, where the sound as an input is only able to provoke a signaling of the nerve terminals, which then in the cortex, controlled by several centers, process the spoken words into meaningful sentences or information, and can even be blanked out (40, 41).

But much as with hearing, not every nociceptive input will generate a meaningful or perceived pain experience (8, 42). And even vice versa (39, 42): the separation goes so far as to be of decisive importance for the pathogenesis and treatment of a certain clinical picture. Central post-stroke pain (CPSP) is a scarcely researched (43), but known since the beginning of the 20th century (44, 45), phenomenon that describes pain that arises centrally after a stroke lesion, primarily found in the ventral posterolateral nucleus (VPL) (i.e., a nucleus of the thalamus) (46). This neuronal hyperexcitability (47), also known as Dejerine-Roussy syndrome or thalamic pain syndrome, leads to a continuous, but sometimes also alternating sharp, stabbing or burning sensation felt in the patient's nociceptively unaffected periphery (45, 48, 49). Please note that CPSP exhibits both nociceptive and neuropathic patterns and can be attributed to mixed pain in the literature (50, 51).

#### **1.1.3.2. Nociceptive neurons**

Nociceptors, as a term for the specialized primary apparatus of pain perception, were for the first time defined by Sherrington in 1906 (52). Peripheral somatic perception, as the first step of pain sensation, predominantly involves 2 types of neurons constituting the primary afferent nociceptors (PAN): Adelta-(A $\delta$ -) and C-fibers (14). They are anatomically distinct (e.g., in diameter or myelination), which physically contributes to their different purposes (8, 14, 21). A $\delta$ -fibers are the smallest thin-myelinated nerves, have a low firing threshold, and a comparatively high conduction velocity of about 30 m/s, made possible by the principle of saltatory conduction (53, 54). The aforementioned characteristics, as well as their small

receptive fields (RF), give them their main function of fast transmission of short-lived “first pain”, which permits a targeted nocifensive response *inter alia* via reflex arcs to effect a rapid withdrawal and sending the CNS an early indication of pain (14, 23, 55). In contrast, the thinner unmyelinated C-fibers allow only a slow conduction speed of up to 2 m/s and their FNE are spread over wider RFs, making them incapable of localizing a stimulus precisely (54, 56). Their main function is to perceive polymodal information (i.e., reacting to various stimuli) and relaying the intensity of a nociceptive input by correlating it with their activation (i.e., encoding a more intense stimulus in a higher frequency of action potentials (57)) (8, 14, 23, 53, 54, 56). The sensed longer-term discomfort is then reported as "dull" (14).

However, the fibers of PAN share several common features. Their perikarya (i.e., somas) are located in DRGs (this is the case for stimuli from the body, please note that fibers innervating the face root in the trigeminal ganglia), which is right at the border to the CNS (8). Each emanates a common axon (a nerve’s fiber), which splits in a pseudounipolar fashion, with one branch towards the spinal dorsal horn in the CNS (the central process) and a peripheral process terminating as “unencapsulated“ FNE in most tissues, such as periosteum (58), vasculature, muscles, and the skin (8, 21). These FNE express a broad and mixed palette of stimuli-sensitive ligand-gated ion channels, G-protein-coupled receptors and voltage-gated sodium (Na<sup>+</sup>), calcium (Ca<sup>2+</sup>), or potassium (K<sup>+</sup>) channels (8, 21), which are the key drivers of excitability by mediating the integration of the generator potential (a process called transduction (23)) and eliciting the electrical all-or-nothing action potentials to later be conducted along the axons (8, 21, 32). Differences and functions of the fiber types are summarized in Table 1. Within the A-fiber group are four subtypes, named from alpha to delta. Please note that Table 1 does not deal with the smaller portion of the two afferent A-subtypes, Abeta- (A $\beta$ -) fibers, as their existence has only recently been proven in humans and it is not yet fully known which contribution this "ultrafast pain system" makes to nociception (59).

**Table 1.** Nociceptors

| Characteristic                   | A $\delta$ -fibers                          | C-fibers   |
|----------------------------------|---|--|
| Function                         | Nociception of "first (fast) pain"          | Nociception of "second pain"   |
| Information                      | Heat, cold, and mechanothermal              | 30% are polymodal (mechanical, thermal, and/or chemical nociception) |
| Thermal sensitivity and receptor | Yes<br>TRPV2 (activated >52°C) <sup>a</sup> | Yes<br>TRPV1 (activated >40°C) <sup>a</sup>                          |
| Myelination                      | Yes   | No   |
| Diameter ( $\mu$ m)              | 2 – 5                                       | 0.02 – 1.5   |
| Conduction speed (m/s)           | 5 – 40                                      | 0.5 – 2  |
| Receptive field                  | Small, well-localized                       | Large, diffuse   |
| Description of sensation         | Pricking "sharp" pain, short lasting        | Dull or "pressing" pain  |
| Other                            | Component of reflex arc                     |  |

Compiled from sources (23, 42, 55, 60–62).

<sup>a</sup> TRPV – Transient receptor potential cation channel subfamily V (vanilloid)

### 1.1.3.3. TRPV1 and ASIC3 receptors

The first step in the mechanism by which physical detrimental environmental influences are recognized is, as already mentioned, transduction (8, 20, 63). It is achieved by molecules present in the FNE that are responsible for the transformation of various energy forms, determining the separation of several types (mainly mechanical-, thermal-, or chemically-sensitive receptors), into electrical action potentials (8, 32, 42, 63). Because a wide spectrum of irritants can activate PANs, only a few may be mentioned here, such as globulins, histamines, growth factors, inflammatory mediators (e.g., prostaglandins, calcitonin gene-related peptide (CGRP), substance P, bradykinin), acidic pH (Latin *pondus hydrogenii* "potential of hydrogen") changes, injury-released ATP or simply extreme thermal conditions. Correspondingly, the

estimated count of receptor families is believed to be as plentiful (56). Much of today's knowledge and ongoing research in this area is mainly confined to two channels, which will be highlighted in the next paragraphs (14, 63). But before that, a word of caution: for molecular and electrophysiological approaches, models of different taxa (including insects, fish, and rodents) and *ex vivo* studies (i.e., cultured neurons lacking extracellular factors and differing gene expression profiles) are generally utilized (14). Even if extrapolation to humans is not always feasible and may be rendered inadequate by future research, phylogenetically conserved findings among various invertebrate and vertebrate species are appreciated and widely accepted in basic research to be true for mammals, as they provide an understanding of the cellular and molecular principles (8, 14, 42, 64, 65). In the dire necessity of superior models, these results deliver important and pioneering insights into what is, at least to some extent, translatable to humans (14).

To begin, acid-sensing ion channels (ASICs) are voltage-independent proton-activated sodium (Na<sup>+</sup>) channels for which five genes in mammals encode protein subunits known as ASIC1–5 (63, 66). These subunits form homotrimeric or heterotrimeric pores, reaching from the surface of the extracellular domains to the axoplasm (67). It might be interesting to note that only ASIC3 and ASIC1b are engaged with nociception (e.g., in inflammation or hypoxia) (34, 63), of which ASIC3 is of special interest (66). This is likely because the PNS expression of ASIC3 was believed to be restricted to PNS sensory neurons at a level that far exceeded other ASIC types, whereas newer research indicates it to be more evenly distributed over the CNS and PNS, and it is found to play a significant role in centrally controlled aggressive and anxiety behavior (34, 66). Another potential reason for the great popularity of this channel is its newly discovered biphasic action in the presence of ongoing extracellular acidity: it only partially inactivates, leaving a sustained current after the initial transient current. As this leads to a prolonged encoding of APs, the ASIC3 becomes a prime target for intervention. Although more than 49 endogenous and exogenous modulators are known to date, no selective antagonist has yet been found that can effectively block both phases. Thus, it remains unclear exactly how ASIC3 affects pain and its physiology (66). The name is already obsolete according to the current literature, since it does not measure protons directly as implied, and instead the activation is rather dependent on gradual changes in the acidic milieu (63, 66). Nevertheless, human ASIC3 has been found to require a pH of 6.0 to trigger cation influx and neuronal depolarization, but in some circumstances less if sensitized primarily by specific mediators that allow already small amounts of protons or other mediators to govern activation at almost pH neutral levels. When the Na<sup>+</sup> influx is adequate enough, APs are triggered through voltage-

gated sodium channels (32). Research has uncovered a COX-independent analgesic mechanism induced by NSAIDs (66). Here, a suppression of the mRNA transcription of selected ASIC subunits was observed. In addition, salicylic acid, aspirin, and diclofenac blocked the sustained current but not the transient one. Conversely, tetracaine, a local anesthetic, inhibits the latter in dependence on pH (66, 68). What can be said with certainty is that operations, fractures, and injuries acutely lead to acid-induced pain via ASICs that lasts for up to four days. It might explain postoperative cutaneous pain and its related behaviors (33, 34).

Then, as a second important receptor, there is the broad family of transient receptor potential (TRP) channels, with more than 30 structurally similar members. The processes they mediate go far beyond nociception, but TRPV1 is considered to be the most important in the (thermal) nociceptive system (14, 42, 63). Located within the cell membrane, the TRPV1 (non-selective cation channel, subfamily V member 1) was obsoletely termed Vanilloid Receptor 1 (VR1), as it is so far the only ion-channel known to be sensitive to capsaicin, a compound possessing a vanillyl group (69). Although capsaicin is a highly effective and selective TRPV1 agonist (63), its activation is also induced by other substances, including but certainly not limited to hypoxic compounds, intense heat, inflammatory processes (prostaglandins, bradykinin), and chemical stimuli like H<sup>+</sup> (i.e., protons), K<sup>+</sup>, and oxygen free radicals (14, 23, 70). The clinical relevance of this is *inter alia* shown in the use of capsaicin as a topical treatment of neuropathic pain due to its selective nature, utilizing the analgesic effect of desensitization (63, 71). Its crucial role in heat detection, yet not solely responsible for it (42), explains the similar “burning” sensation experienced by the mentioned noxae. Studies in knockout animals, lacking TRPV1, but with continuance of heat nociception, show a redundancy, implicating the high level of evolution and complexity of the mammalian nociceptive system (69). In the case of excitation by an increased temperature (>43°C) or other previously mentioned stimuli, the cation channel opens in a stepwise fashion by conformational changes in the protein subunits (i.e., the physical structure). The outer pore domain most likely undergoes heat-activated domain motions, opening the selectivity filter on the outer aspect for influx together with the allosterically coupled lower gate modification for subsequent pore opening. At negative holding potentials of around -60 mV, this activation causes the pore to open just wide enough to allow calcium (Ca<sup>2+</sup>) and sodium (Na<sup>+</sup>) influx, thereby depolarizing the cell toward a positive threshold potential (14, 72, 73).



#### 1.1.3.4. Neural pain pathways

As mentioned earlier, human nociception, if ever fully elucidated, will be more complex than what has been discovered through animal or specimen studies. In the field of anatomy and physiology, combined endeavors from neuroanatomical, physiological, psychological, and pharmacological research have already made such great strides as to limit the present study to only an illustrative pathway, which provides enough similarity to the others in order to identify the cornerstones: somatic cutaneous nociception. Other studies have well-characterized the similarities and differences in additional nociception pathways such as visceral, musculoarticular, and articular pain (74–76). Consider simple damage to the extremities (e.g., a cut on the hand, a burn on the calf) as an approach to exploring this general overview of the "classical" route.

To follow up on the previous section, after transduction has taken place, we begin by triggering a sufficient generator potential in the FNE. The opening of ion channels permeable to specific ions will result in the membrane potential shifting in the positive direction (depolarization) since the electrochemical gradients for sodium ( $\text{Na}^+$ ), calcium ( $\text{Ca}^{+2}$ ), and chloride ( $\text{Cl}^-$ ) are more positive than the resting potential (8, 32). Thus, they trigger the activation threshold for voltage-gated  $\text{Na}^+$  channels ( $\text{NaV}$ ) and induce an action potential, or more commonly, a series of them (32, 56). The AP is conducted along the axons of the first-order neurons of the PAN towards the CNS. Referred to are again the  $\text{A}\delta$ - and C-fibers, whose somas are clustered in the DRG (23, 56, 77). Note that in the case of facial nociceptors, these somas are principally located in the trigeminal ganglion (TG) (8, 23, 56). The afferent signals at the peripheral end of these pseudounipolar neurons are carried away in a step called conduction towards the central branch and are brought into the spinal cord through the dorsal root (8, 54, 78). It is thought that a small proportion of the fibers diverge cranially and caudally for several segments of the spinal column in the Lissauer tract (dorsolateral fasciculus) before entering the dorsal horn of the gray matter (79–81). In the dorsal horn or, for facial nerves, in the trigeminal subnucleus caudalis, the PAN synapses with dendrites of second-order neurons by neurotransmitter release (8, 21, 23). These postsynaptic neurons are either “ $\text{A}\delta$ -specific neurons” or wide dynamic range (WDR) neurons (i.e., capable of transmitting graded potentials), the latter responding to both, glutamate released by  $\text{A}\delta$ -fibers, acting on alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors, and the C-fibers-released neuropeptide substance P, activating neurokinin-1 receptors (8, 23, 56, 78).

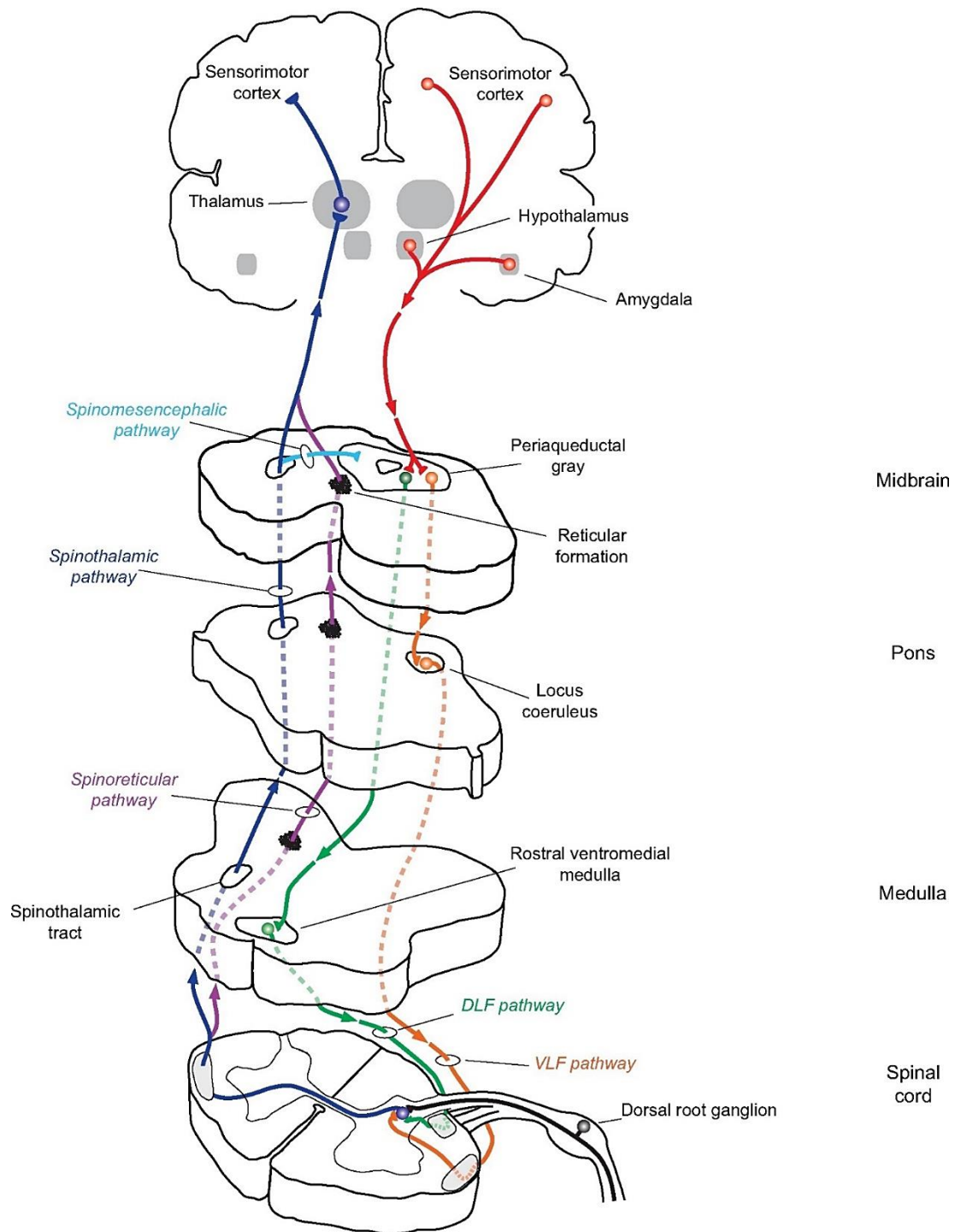
The second-order neurons in the dorsal horn send their axons over the midline while passing through the anterior white commissure into the contralateral ventral aspect within the white matter, an area referred to as the spinothalamic tract (STT) (78, 82). The STT, also known as the anterolateral or ventrolateral system, is the primary fiber projection that conveys nociceptive, thermal, and tactile stimuli to the VPN and intralaminar nuclei, among other thalamic nuclei (23, 56, 78, 82).

For further processing of information, localization and ultimately perception of pain, the ventral posterolateral nucleus and the ventral posterior inferior nucleus give rise to third-order neurons (56), sprouting their axons to the somatosensory cortex in the forebrain and many other higher centers, which are conjointly denoted as the “pain matrix” or neuromatrix (11, 21, 56, 78, 82, 83). Furthermore, to establish an integration of these signals into emotional responses and to generate nocifensive behaviors toward threats, fibers from the ventral quadrant of the spinal cord also end up, via third-order neurons in the ventromedial hypothalamus and medial regions of the thalamus, in (para-)limbic portions of the neuromatrix, as the anterior cingulate cortex (ACC) or insula cortex (84, 85). The ACC lies in direct connecting positions to the prefrontal cortex (86) and thus provides us with the cognitive-affective connotations of pain (emotional response to pain) (26, 87), while the insula serves as the primary regulator of empathy for another person's sorrow (88) or the ability to envision pain in ourselves when we see pictures of traumatic occurrences (89).

Running in the opposite direction to the ascending pathway, there are two equally important central systems that allow us to modulate afferent pain directly from within our body (56, 82, 90). For one, there is the gate control theory (GCT) locally at the spinal entry level of a nociceptive input and, in addition to it, a supraspinally controlled downward modulation (19, 21, 78, 82). From a historical perspective, we have come a long way with many different postulated ideas, which finally led us to the most widespread and used one today, as it was able to bridge the key features of the previously prevailing theories and prove itself, despite the technological limitations at that time, through modern development (19, 90). Originally published in 1965 by Melzack and Wall simply as "A new theory", the GCT respected the already experimentally proven evidence of the "Specificity" (or labeled line) and "Pattern" theories and was capable of matching rivalling results, ending a century old discussion on which is more accurate (19, 91, 92). It introduced additional neurons in the dorsal horn to those already described above. More specifically, inhibitory interneurons, located in Rexed Lamina II (also called substantia gelatinosa), the location in which a majority of PAN fibers synapse to the STT cell bodies (93, 94). This area is called “the gate”. Because non-nociceptive neurons transmit

sensory signals through the dorsal horn, which here collaterally branch to excite interneurons, that in turn deliver inhibitory neurotransmitters (e.g., gamma-aminobutyric acid (GABA)) to the pre- and postsynaptic membranes of the PAN and WDR neurons, it is possible to alleviate pain through non-painful inputs such as deep touch, skin rubbing, and hot or cold packs (78, 93–95). The result is a decreased release of excitatory neurotransmitters from first-order neurons (predominantly C-Fibers) and the reduced transmission of AP along the STT (78).

The second system, the descending analgesic system, as the name implies, is controlled from above and includes several cortex and midbrain structures that cause pain relief on the level of the dorsal horn as well (78). For instance, it is triggered by derivative fibers of the STT, the cortex, or hypothalamus to the periaqueductal gray (PAG) or periventricular gray matter (PVG). PAG and PVG act on nuclei of the midbrain, e.g., the rostroventral medulla or locus coeruleus, which are rich in serotonin (5-hydroxytryptamine (5-HT)) and norepinephrine, respectively. These send their signal down to another set of inhibitory interneurons located in the lamina II, and induce endogenous opioid (enkephalins, endor-, and dynorphins) release (26, 56, 82, 83, 93). At the spinal cord level, opioids operate as ligands for opioid receptors, activating them to produce cell hyperpolarization by opening potassium channels and inhibiting calcium influx (26). Action of substance P is subsequently suppressed, which limits the upward propagation of pain (56). In Figure 1, the described pathways are illustrated schematically (82), excluding the involvement of the GCT in the dorsal horn.



**Figure 1.** Ascending and descending nociceptive tracts: First-order neurons of the PAN (black tract) entering the dorsal horn of the spinal gray matter via the dorsal root. Neurotransmission of signals to second-order neurons of the spinothalamic tract (STT; blue), cross via the anterior white commissure, then ascending in the now contralateral spinothalamic fasciculus in the anterior white column, conducting to third-order neurons in the thalamic nuclei. Modulating information is sent downwards by descending pathways from the brain, hypothalamus, and amygdala to the periaqueductal gray (PAG) inside the brainstem (red tract).

[Special thanks to the originator for granting permission to use (82)]

#### **1.1.4. Influencing factors to pain**

At this point, it has certainly surfaced that pain is an integral part of an individual's nature, complex and highly influenceable. However, these factors do not only include intrinsic or extrinsic measures such as medication or non-invasive therapies. A lot of endeavors have been devoted to the study of developmental and demographic determinants, some of which will be highlighted in the following section. These factors show that perceived intensity and individual sensation are by no means directly correlated with the stimulus per se, but are subject to a multitude of variables on all levels of the processes that take place (physical sensory nociception, emotional response, and countermeasure), affecting both acute and chronic states and the progression from one to the other (96, 97). These include genetic, familial, psychological (e.g., depression in combination with anxiety), sociocultural, and situational (e.g., evident in consensual sadomasochistic erotic behavior (96)) aspects, as well as the attention and expectations of each individual (97, 98). Perception may be impaired by stress or enhanced by expectation to such an extent that it may disturb the effectiveness of analgesia and require personalized and interdisciplinary therapies (8, 27). The extremes, such as having no pain sensations at all because of a genetic pathological condition, up to having pain in missing limbs (also termed “phantom pain”), are the boundaries of a spectrum that once again emphasizes the multifactorial basis of this problem (98, 99).

One might be tempted to see gender as a clear and primary predictor, as so often in other conditions. However, disagreement among researchers for the past decades has demonstrated that this assumption is difficult to prove, or at least to root back to its causes (100). Sex differences in the functionality of nociceptors are shown in preclinical models, as well as increasingly in more recent human studies (77). Although there is gender-dependent variance in how humans perceive pain, it has not yet been sufficiently connected to corresponding biological variations in nociceptors (77). Regardless, it can already be said that there is an unequal distribution between the sexes, with women experiencing more pain and suffering (96, 101). Furthermore, they have a higher prevalence of the most frequent forms of pain (100) and of anxiety and depression (96), exhibiting elevated susceptibility to experimentally elicited pain (100), and have higher average numeric pain scores as well as a 14–16% higher incidence of postoperative pain events on the first day after a wide range of surgical modalities (102). Interestingly, preliminary data from a recent study shows that gender identity rather than genetic sex might have an impact on pain perception. The results, albeit constrained by a set of study limitations, show that transwomen respond similarly to ciswomen in response to nociceptive pain stimuli (103).

The mostly ambiguous knowledge about age also indicates that we are only in the early phase of our search for influencing factors (77, 104). Studies have found "young age" in adults to be an independent risk factor for higher pain intensity (101, 105, 106), in opposition to a meta-analysis conducted in 2017 by El Tumi et al., with the conclusion that the direction of the significant differences between young and old was discordant (104). A meta-analysis by Lautenbacher et al., published in the same year, addressed the question of pain thresholds and concluded that being of older age is associated with reduced pain sensitivity (107). El Tumi et al. also compared three studies showing that in individuals under 18 years of age, younger children had higher sensitivity to pain than older children, with a changeover at 9 years (104). Contradicting these findings, a study by Galai et al. in 2020 with 284 pediatric patients found that older children reported a higher postprocedure level of pain after endoscopies (108). Recalling the previous paragraph, Galai et al. did not find any significant gender-differences in these children (108). The association of age with the length of stay (LOS) in PACU is not consistent among literature (109).

Despite the efforts, each person's interpretation of pain and how it manifests will remain greatly dependent on their conscious experience, personal history, psychological setting, and the value of the pain to themselves (110).

## **1.2. Anesthesiology**

The first successful safe and effectively painless operation under inhaled ether anesthesia, performed by dentist William T.G. Morton and general surgeon John Collins Warren on October 16, 1846, marked a milestone on which modern anesthesiology and surgical medicine in general are based (4).

The name of this medical specialty is rooted in the Ancient Greek words *an-*, "not", *asthesis*, "sensation", and *-logia*, "study" and is thus literally the science of non-sensation (111). The absence of pain in response to stimuli that would usually elicit pain is referred to as analgesia and constitutes one of the major concerns of any anesthesiologist. But their role also encompasses perioperative care (Ancient Greek: *peri-*, "around", including before (preoperative), during (intraoperative) and after an operation (postoperative)), intensive care, and emergency medicine, and is growing to include other tasks such as the administrative leadership and involvement in clinics or the health care system (112, 113). This demonstrates that the anesthesiologist's work is not confined to the time of the operation; quite the contrary, they are particularly responsible for patient safety in accordance with the "Helsinki Declaration on patient safety" and generally acknowledged as those in charge of it (112, 114).

### **1.2.1. Postanesthesia care unit**

An anesthesiologist's treatment of the patient during any form of surgery does not end when the patient leaves the operating room (OR). As it is common practice in most European countries, the patient is taken immediately, but temporarily, from the OR to the usually adjacent recovery room, where the surgical and anesthesiological follow-up takes place, hence the name "post-anesthesia care unit" (PACU). These units, a concept firstly introduced in 1923 (115), represent the direct interim of several hours for almost all patients between surgery and discharge to the peripheral wards, with the ultimate goal of minimalizing morbidity and mortality (115–118). The necessary follow-up (i.e., postanesthesia care) is individual for every patient, but still includes certain standards to warrant safety and high quality. The primary objective is the early detection of any complications and the avoidance of preventable sequelae, as well as permanent damage of mental, neurological, cardiological or similar nature, provoked by the surgical or anesthetic intervention (116, 117).

The main instrument of the PACU is the continuous monitoring and an extended number of nursing staff and physicians (115, 116). There are no international standards that define this, but there are a number of guidelines according to which each institution has to define the appropriate directives for themselves (116, 117). This also includes the proper training, equipment and guarantee of the PACU's functions. Specialized medical staff are responsible for the management of the patient's condition and should be able to initiate adequate and optimized pain management immediately after surgery, determine triage to different units (including intensive care unit (ICU), high-dependency unit or normal wards, and in some cases discharge home), maintain all vital functions, and intervene immediately if problems are recognized (116). Continuous monitoring includes not only the measurable values such as oxygen saturation, blood pressure, heart rate, temperature and an electrocardiogram (ECG), but also the evaluation and recording of mental alertness, pain condition and the control of postoperative nausea and vomiting (PONV) and bleeding. In addition, certain circumstances may require recording of capnography (e.g., in ventilated patients) or assessment of neuromuscular functions (116, 117, 119). Regular evaluation of respiratory rate and airway patency, as well as the establishment of normothermia is equally indispensable (117). Observation should continue at least until the patient is no longer at risk of cardiorespiratory complications. Please note, that evidence is insufficient to assess the advantages of enforcing a minimum stay till discharge from the PACU. An obligatory minimum stay is advised against by experts, as the duration of stay should be decided solely on a case-by-case rationale, taking specific discharge criteria into account (116, 117). These are by no means fixed nor unified

among institutions, and there is no validated golden standard either (115). Studies from several countries calculated the times a patient stays in the PACU with different start and end points, producing mixed results of means ranging from 60 minutes to 3.5 hours (109, 115, 119, 120). It is equally difficult for them and health care providers to determine when a patient has been in the PACU for "too long", regardless of the decisive reasons (109). For the plethora of surgical procedures and concomitant anesthetic methods, there are no established reference values for the proper PACU length of stay (LOS) (115).

The LOS in the PACU is distinct for each patient and found to be influence by a wide range of factors. These include among others insufficient postoperative pain management (121), surgical time, anesthetic technique, time under anesthesia (115, 122), pain level, occurrence of PONV (119), and critical pulmonary or cardiac adverse events (123). Contrary to this, adjuvant dexamethasone has shown exploitable properties that can reduce postoperative pain scores and opioid-use, consequently shortening stays in the PACU (118). A study by Mann-Farrar et al. in 2019 found an association between prolonged PACU LOS with an increased incidence of clinical worsening of the patients, but they also noted a higher age and American Society of Anesthesiologists (ASA) score in the group of interest (120, 124). An earlier study could not observe any significant association between PACU LOS and age, ASA score or gender (115). Interestingly, similar to a 20 years later conducted study, aforementioned study found the time the patient spent under anesthesia, which in a simplified sense is almost the same as the surgical time, to be correlating by a positive factor. With significant results, both studies show the influence on LOS in PACU by the previously spend time in the OR, in one of them for example to be around a median ratio of 1.5 (i.e., PACU time is one and a half times as long as the surgery time) (115, 122).

While most are justified and in the best interests of the patient, an unnecessarily prolonged stay in PACU creates a heavy financial burden with several micro- and macroeconomic consequences, not to mention concerns for the patient's safety and care. A practical objective can be to avoid peaks in the volume of patients in the recovery room to facilitate a continuum of flow, thus prevent accumulation and bottlenecks in care provision. These would back up into the OR, as the PACU cannot accept any more patients when overloaded, and in the worst-case scenario not even those who are in life-threatening peril and require urgent emergency intervention (109, 119). Furthermore, an optimized flow reduces the workload on nursing staff, improve the surgical schedule and increase satisfaction of surgeons, patients and their relatives (109, 125).



### **1.2.2. Pain management**

The access to and reception of high-quality pain management is seen by many as a fundamental human right (126, 127), but should still be promoted as such under the consideration of biological, ethical and economic justification (128).

Pain in a clinical setting can be, as previously mentioned, the consequence of surgical stimuli and invoke an interaction between the surgical incision itself and previous patient-related conditions, triggering a cascade of neuromodulation, inflammation, and central and peripheral sensitization that amplifies and prolongs postoperative pain even past the point of actual recovery (22, 33, 53, 129). Postoperative pain affects over 80% of surgery patients, and when it is not properly treated, it can have a multitude of adverse effects, such as a detrimental impact on income and employment, the development of mood disorders, on cognitive functions (e.g., poor memory, lack of focus, and the inability to accomplish mental skills), and consequently on the overall quality of life (27, 118). Furthermore, it is associated with a negative impact on patient recovery and satisfaction, as well as an increase in health care system costs (121, 130). Identical outcomes are seen when postoperative pain scores are elevated and include decreased patient satisfaction, postponed recovery, the development of chronic pain, and higher rates of morbidity and mortality (105).

Appropriate preventive measures, which should, whenever feasible, take into account all potential pitfalls, are the key to avoiding these unfavorable postoperative outcomes, and should be started early on in the surgical process. They include education, early recognition and diagnosis and aggressive analgesic treatment by means of a multidisciplinary strategy that combines medication and complementing non-pharmacological approaches (121). In this context it is important to acknowledge that the mode of anesthesia (115), the specific conducted type of surgical procedure (also reflected in the extend of tissue injury) (102, 109, 119, 131), as well as the individual's idiosyncratic reaction to analgesia vary greatly in intensity and change the nociception and perception of noxious stimuli (102).

Typically, the anesthesiologist conducts a preoperative evaluation of the patient on the day before surgery, reviewing the medication plan, medical records, the most recent blood values, the patient's physical status, and assesses risk scores such as the ASA score (132). In some cases, the attending specialist may decide it is necessary to support the regular general anesthesia with “preemptive analgesia”. In this form of analgesia, different techniques are applied just before the surgical procedure (before the incision), with the idea to interrupt processing along the pathway and the aim to avoid central and peripheral sensitization (130, 133, 134). Rather than treating the consequence, the rationale is, and experimental evidence

support that, to forestall (i.e., “pre-empt”) the neurophysiological and biochemical sequelae of damaging CNS exposures (134). Studies have shown that phantom limb pain was reduced when epidural or systemic analgesia was applied under induced narcosis before the sensitizing stimulus instead of the identical treatment after the stimulus (130). Nonetheless, its usefulness remains a matter of debate (133, 135), as it could also be seen as part of a much more general, overarching concept: in "preventive analgesia", the exact timing of treatment is of less importance (135). It has the aim to reduce sensitization to unpleasant stimuli that occur during the entire perioperative course, meaning analgesic interventions done at any time (133).

In the next phase, namely the intraoperative management, the most frequently used approach to analgesia is a multimodal regimen (83). It is widely considered to be the most effective and may also be referred to as "balanced analgesia" (130, 136). It is hallmarked by the utilization of several drugs (opioids and non-opioids) with distinct mechanisms of action, achieving a synergistic effect that leads to a reduction in quantity requirements ("opioid-sparing") and a stronger deceleration of the pain transmission (83, 130, 133, 135). Various anti-nociceptive agents are used in parallel, as well as local anesthetics, NSAIDs, NMDA antagonists (ketamine),  $\alpha$ -2 agonists (gabapentin) and selective COX-2 inhibitors, capable to enhance or inhibit the action of endogenous neurotransmitters (i.e., GABA, substance P) (130, 133, 135, 137). As a result, the frequent side effects of opioids such as nausea or ileus can be minimized in the postoperative period, which would otherwise lengthen the healing process, resulting in a prolonged hospital stay and higher expenditures for the health care systems (130, 137). Furthermore, this technique proved beneficial in averting nociceptive disturbances, which are an important cause of intraoperative hemodynamic and stress-induced sympathetic instability, and chronic pain syndromes (83). Recent studies conducted in 2020 and 2021 using sufentanil (a synthetic opioid acting primarily on  $\mu$ -opioid receptors) and serotonin-norepinephrine reuptake inhibitors (SNRIs) respectively, in addition to standard perioperative treatment, demonstrated marked reductions in postoperative pain, opioid-sparing effects, and relief of stress and inflammatory responses, without a rise in adverse outcomes (138, 139). Likewise, in 2012, Abdulla et al. found that patients before discharged from the PACU had a smaller need for piritramide when used in conjunction with intravenous metamizole (140). One perioperative intravenous injection of dexamethasone offered significant analgesic advantages, according to another meta-analysis, with lower pain scores, a reduced need for opioids, and a shorter PACU LOS (141). Although often used synonymously in clinical and scientific parlance, please note the distinction between balanced analgesia and balanced anesthesia. The latter usually describes the combination of a volatile hypnotic agent (such as the ether

anesthetics desflurane and sevoflurane) with an opioid to achieve a reversible state of insensibility by unconsciousness, among other mechanisms (83, 142). Analgesia remains merely the relief of pain itself and, like motor paralysis, amnesia and unconsciousness (which must not mandatorily all be present at once), can be considered a part of general anesthesia (83, 142, 143). However, in certain patients, the use of inhalational drugs is contraindicated or simply impractical, so the general anesthetic state is achieved by total intravenous anesthesia (TIVA), in which the volatile agent is substituted for an intravenously administered hypnotic (e.g., propofol) (83, 144).

Finally, postoperative care is extensive and expensive because different components must operate effectively. These include relationships between the OR, PACU, and ICU, as well as hospital bed availability, necessitating a dynamic system (109). To provide proper postoperative pain control, the multimodal approach must continue in the postsurgical and post-discharge phases, as well as be integrated into an interdisciplinary and comprehensive care (83, 130). To assess the amount of pain the awake and conscious patient is experiencing, they are in most scenarios asked to indicate it on a one-dimensional scale of 0 to 10, with 0 representing “no pain at all” and 10 representing the “most unbearable pain imaginable”. This rating is called a numeric rating scale (NRS) and helps determine a subjective self-reported PACU pain score. Significantly correlating to the NRS, a verbal rating scale (VRS) is ranking pain by asking the patient to categorize it from “none” (NRS=0), over “mild” (1-4) or “moderate” (5-7) to “severe” (8-10) (145). Because all of the above-mentioned factors impact one's personal perception of pain, it is not surprising that these simple methods have been heavily criticized since they were first introduced (102). Nevertheless, NRS remains the most commonly used, validated and universally-known golden standard of pain scoring in adults and therefore occupies a unique place in research to this day (102, 118). Another, already mentioned, drawback is the fact that the patient must be awake and have the understanding to clearly vocalize his pain level. As this proved complicated in pediatric, mentally challenged, or other non-verbal patients, Visual Analogue Scales (VAS) have also developed in parallel, based on the same principle of grading from low to high, but using cartoons of anguished faces. Derived from this are both the Wong-Baker FACES Pain Rating Scale and the Hicks' Faces Pain Scale revised (FPS-R), which have been validated for use in 5-12- and 3-18-years old patients, respectively (146, 147). Another interesting take with good sensitivity (0.92 – 0.96) is the by Büttner et al. developed Children's and Infants' Postoperative Pain Scale (CHIPPS), which is based on external observations, made by the attending medical staff, such as crying, grimacing, or trunk posture (148).

## **2. OBJECTIVES**

## **2.1. Aim**

The aim of this study was to investigate the influence on the length of stay (LOS) within the post-anesthetic care unit (PACU) and to determine whether postsurgical pain scores or body weight could serve as predictors of its length.

## **2.2. Hypothesis**

1. There is no significant relationship between BMI and LOS in PACU.
2. There is no significant relationship between first measured NRS and LOS in PACU.

### **3. MATERIALS AND METHODS**

### **3.1. Ethical approval**

The Institutional Review Board of the Medical School Regiomed Coburg approved this research project on March 25, 2022, and study registration was not required given the retrospective nature of this project.

### **3.2. Subjects and data collection**

In this retrospective single-centered cross-sectional study, we included 283 patients' data who were undergoing surgery in the REGIOMED Hospital Coburg, Germany in a time period from November 2021 to March 2022. The resulting dataset remains deidentified and does not contain any personal patient-related information. Included were all adult patients who underwent a form of anesthesia within the scope of their surgery and had a subsequent stay in PACU. Therefore, any patient under the age of 18, as well as patients who were transferred to another ward (e.g., intensive care unit) were excluded.

### **3.3. Measurements of the outcome**

To measure the outcome, anthropometric measurements of height and weight were used to calculate the body mass index (BMI; kg/m<sup>2</sup>), additionally NRS, age, gender, and the LOS in PACU were obtained from the perioperative anesthesia record sheet. Furthermore, from the same document, the conducted type of surgery and anesthesia, the patient's previous status as a chronic pain patient and ASA score when available, the analgesic medication used in OR and PACU, the occurrence of PONV, as well as the time spend in OR were noted.

### **3.4. Methods and definitions**

For the sake of comparability of different treatments and surgical procedures we converted the cumulative analgesic drugs by specific conversion factors according to equianalgesic dose ratio tables to intravenous morphine equivalents, visible in Table 2. We would like to point out explicitly that there are considerable limitations and criticism regarding the use of equianalgesic conversions and tables (149–151). They should generally be used with caution and we strongly advise against the use of our version in clinical practice or decision making (151, 152). A subsequent calculation of relative opioid demand (i.e., consumption) was made on the basis of morphine equivalence in milligrams (mg) over 60 minutes (i.e., mg/1 hr), both in OR and in PACU. The adjunctive use of non-opioid analgesics, such as metamizole or dexketoprofen, improve PACU pain scores, but cannot be readily calculated (153, 154).

**Table 2.** Approximate parenteral equivalence dose conversation factors

| <b>Analgesic</b> | <b>Factor</b> | <b>Equivalent dose in milligram (mg)</b> | <b>Reference</b> |
|------------------|---------------|--|------------------|
| Morphine         | 1             | 10 mg                                    | –                |
| Alfentanil       | 10            | 1 mg                                     | (155–157)        |
| Fentanyl         | 100           | 0.1 mg                                   | (156, 158, 159)  |
| Remifentanil     | 200           | 0.2 mg                                   | (160, 161)       |
| Sufentanil       | 1000          | 0.01 mg                                  | (156, 162–164)   |
| Piritramide      | 0.7           | 14.3 mg                                  | (165)            |

Data accumulated according to sources in column “Reference”.

In the first step, the whole data set without subcategorization was analyzed and described. Descriptive as well as inferential statistics were performed on either the whole set and on stratified subgroups based on the whole sample.

Several subgroups are categorized on basis of the following: according to the ASA classification (Class I–VI), eight surgical specialties (seen in Table 9 in section Results), four anesthesia techniques (TIVA, balanced, analgosedation, and local nerve blockade), and history of chronic pain. Subgroups smaller than 20 will not be used for statistical calculations, with the exception in the comparison of PONV subgroups. The 11-item NRS (ranging 0-10 scale), the LOS in PACU in minutes, and the BMI are used in a linear manner. For the latter, the world health organization defines specific cut-off values for adults in different nutritional statuses, shortened and listed in Table 3 (166). In addition, the NRS was divided into ordinal categories corresponding to the VRS (“none”, “mild”, “moderate”, and “severe”), determined with cut-off values defined by Lee et al. in 2021 (145).

**Table 3.** Nutritional status

| <b>BMI (kg/m<sup>2</sup>)</b> | <b>Nutritional status</b> |
|-------------------------------|---------------------------|
| <18.5                         | Underweight               |
| 18.5 – 24.9                   | Normal weight             |
| 25 – 29.9                     | Overweight                |
| >30                           | Obesity                   |

According to source: <https://www.who.int/europe/news-room/fact-sheets/item/a-healthy-lifestyle---who-recommendations> (date accessed: 18.07.2022)



### 3.5. Statistical analysis

The statistical analyses were performed using JASP (JASP Team (2022). JASP (Version 0.16.3) [Computer software], Amsterdam, Netherlands). Categorical data is presented as numbers (N) and percentages (%), and continuous data is reported as mean  $\pm$  standard deviation ( $\pm$ SD) or median (IQR=interquartile range), when appropriate. In order to test for normality in the sample and among groups, the Shapiro-Wilk test was used. Non-normally distributed data was compared with the Mann-Whitney-U test in the case of ordinal or continuous variables in two groups, and in order to determine the difference between three or more groups a Kruskal-Wallis test was used instead. In the case of a significant outcome on the latter, a *post hoc* Dunn's test was conducted in selected instances. For bivariate analysis of non-parametric data, correlation coefficients were computed with Kendall's Tau-b ( $\tau_b$ ) and Spearman's Rho ( $\rho$ ). For all models, a significance P-value cut-off of  $P < 0.05$  was set.

## **4. RESULTS**

The study included 283 patients who underwent various forms surgery under some kind of anesthetic procedure with a subsequent stay in the PACU. The mean age of our whole study group was 59.6 ( $\pm 17.6$ ) years, with a minimum of 18 and a maximum of 91 years, and a gender distribution of 163 women and 120 men (57.6% vs 42.4%, respectively). Specifically, the median age in women was 63.0 (IQR=22.5) years, while men had a median age of 59.0 (IQR=27.25) years, without any difference between genders ( $p=.580$ ; Mann-Whitney U). The mean BMI was 28.9 ( $\pm 6.1$ ) (N=277), and the median was 28.1 (IQR=9) and 27.0 (IQR=5.85), in women and men, respectively, yet again showing no significant difference ( $p=.439$ ; Mann-Whitney U). 28 patients (9.9%) were classified as chronic pain patients, 16 of which were female and 12 were men. All 9 patients (3.1%) experiencing PONV in the PACU were of female gender. These and additional characteristics of the sample are summarized in Table 4.

**Table 4.** Descriptive statistics of continuous and integer variables of total sample (N=283)

| Variables                                   | Category          | N   | %    | Mean $\pm$ SD    |
|---|-------------------|-----|------|------------------|
| Age (years)                                 |                   | 283 |      | 59.6 $\pm$ 17.6  |
| Gender:                                     | Female            | 163 | 57.6 |                  |
|   | Male              | 120 | 42.4 |                  |
| BMI (kg/m <sup>2</sup> )                    |                   | 277 |      | 28.9 $\pm$ 6.1   |
| Chronic Pain Patient                        |                   | 28  | 9.9  |                  |
| Type of anesthesia:                         | Balanced          | 249 | 88.0 |                  |
|   | TIVA <sup>a</sup> | 31  | 11.0 |                  |
|   | Nerve Block       | 2   | 0.7  |                  |
|   | Analgo-sedation   | 1   | 0.3  |                  |
| Total time in OR <sup>b</sup> (min)         |                   | 283 |      | 74.8 $\pm$ 43.3  |
| Total LOS in PACU <sup>c</sup> (min)        |                   | 283 |      | 114.0 $\pm$ 50.7 |
| Discomfort:                                 | PONV <sup>d</sup> | 9   | 3.1  |                  |
|   | Shivering         | -   | -    |                  |
| First NRS <sup>e</sup> in PACU <sup>c</sup> |                   | 259 |      | 3.4 $\pm$ 2.8    |
| Discharge NRS <sup>e</sup>                  |                   | 252 |      | 0.9 $\pm$ 1.2    |

Data are presented as number of participants (N), as percentage (%) and as mean  $\pm$ standard deviation (mean  $\pm$  SD).

<sup>a</sup> Total intravenous anesthesia

<sup>b</sup> Operating room

<sup>c</sup> Post-anesthesia care unit

<sup>d</sup> Postoperative nausea and vomiting

<sup>e</sup> Numerical Rating Scale, 0 to 10 integers

For a first analysis of possible correlations in the whole group, the dependent variable (PACU LOS) was contrasted with the independent variables (BMI and First NRS), all of which can be seen in Table 5. In addition, opioid demand in PACU was examined for associations to these parameters. We found a significant positive (monotonic) correlation between time spent in the PACU and the first NRS collected from patients,  $r_s(257) = 0.295$ ,  $p < .001$ . However, there was no correlation between body weight measured by BMI and time spent in PACU,  $r_s(275) = 0.028$ ,  $p = 0.642$ . We found that regarding the opioid demand in PACU, there was a strong positive significant correlation to the first NRS of  $r_s(257) = 0.695$ ,  $p < .001$ , and a slight positive correlation to the LOS,  $r_s(281) = 0.124$ ,  $p = 0.037$ . Again, the BMI showed no correlation to this value,  $r_s(275) = 0.010$ ,  $p = 0.866$ .

**Table 5.** Rank correlation of outcome measures regarding the total sample (N=283)

| Parameters                                     | N   | Rank correlation coefficients |          |                              |          |
|--|-----|-------------------------------|----------|------------------------------|----------|
|  |     | Spearman's<br>(rho) $\rho$    | <i>P</i> | Kendall's<br>(tau) $\tau$ -b | <i>P</i> |
| PACU LOS <sup>a</sup> x First NRS <sup>b</sup> | 259 | 0.295                         | < .001   | 0.218                        | < .001   |
| PACU LOS <sup>a</sup> x BMI <sup>c</sup>       | 277 | 0.028                         | .642     | 0.020                        | .629     |
| PACU LOS <sup>a</sup> x Opioid demand          | 283 | 0.124                         | .037     | 0.082                        | .052     |
| Opioid demand x First NRS <sup>b</sup>         | 259 | 0.695                         | < .001   | 0.547                        | < .001   |
| Opioid demand x BMI <sup>c</sup>               | 277 | 0.010                         | .866     | 0.006                        | .894     |

Data are presented as number of participants (N). Significant P-values are bold.

<sup>a</sup> Post-anesthetic care unit length of stay

<sup>b</sup> Numerical Rating Scale

<sup>c</sup> Body Mass Index

The personal perceived level of pain can be expressed in either a numerical value (NRS) as well as an analogue verbal category (i.e., VRS), on which basis we addressed if it is likely that the previous significant observations are greater in one category than in the groups following by increasing severity. Indeed, as shown in Table 6 and Figure 2, there was a significant difference in median times across the four severity groups (N=259),  $H(3) = 20.695$ ,  $p < .001$ ,  $\eta^2 = 0.08$ . According to a subsequent *post hoc* Dunn test, we revealed there was no significantly shorter LOS in the “None” group than in the “Mild” group ( $p = 0.062$ ), but in the “Moderate” and “Severe” groups ( $p < .001$  in both). LOS for “Mild” in comparison to “Moderate” and “Severe” were also significantly shorter ( $p = 0.039$  and  $p = 0.002$ , respectively). The stay of “Moderate” was likewise significantly shorter than in the “Severe” group ( $p = 0.039$ ). Regarding the median BMI, the distribution was similar among the groups ( $p = 0.986$ ).

**Table 6.** Comparison of medians of PACU LOS and BMI among VRS categories adapted from NRS according to Lee et al. (145)

| Parameters                               | VRS <sup>a</sup> (NRS <sup>b</sup> ) categories |                        |                            |                           | P*     |
|--|---|------------------------|----------------------------|---------------------------|--------|
|  | None (0)<br>(N = 80)                            | Mild (1-4)<br>(N = 72) | Moderate<br>(5-7) (N = 87) | Severe (8-10)<br>(N = 20) |        |
| PACU<br>LOS <sup>c</sup> (min)           | 85.0<br>(IQR=50)                                | 95.0<br>(IQR=60)       | 115.0<br>(IQR=50)          | 147.5<br>(IQR=92.5)       | < .001 |
| BMI <sup>d</sup><br>(kg/m <sup>2</sup> ) | 27.4<br>(IQR=6.95)                              | 28.1<br>(IQR=6.9)      | 28.0<br>(IQR=7.5)          | 28.0<br>(IQR=7.2)         | .986   |

Data are presented as median with interquartile range (median (IQR)).

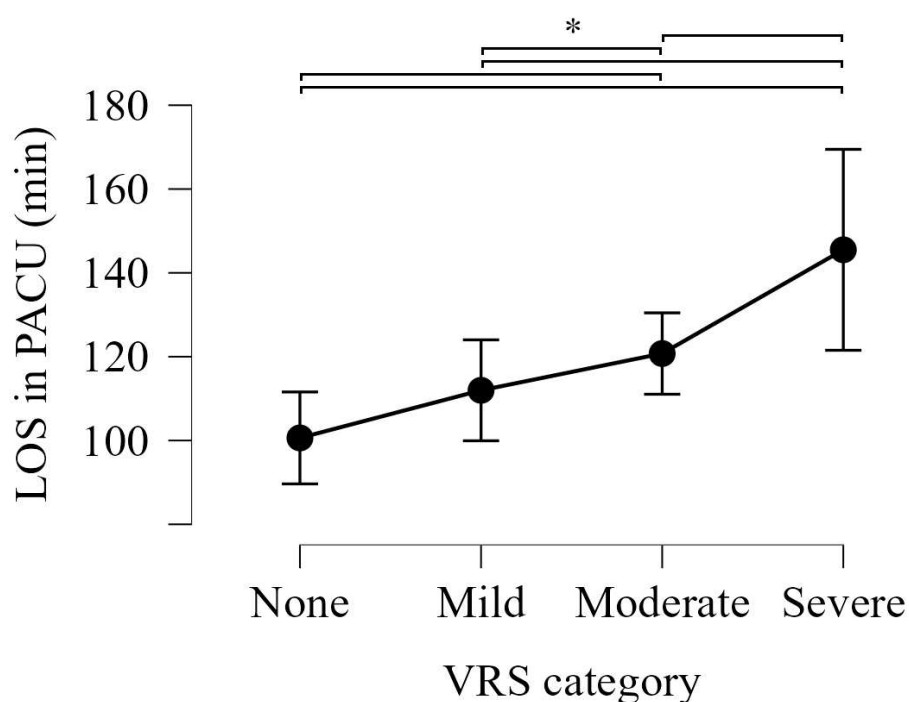
\* Kruskal-Wallis H Test

<sup>a</sup> Verbal Rating Scale

<sup>b</sup> Numeric Rating Scale

<sup>c</sup> Post-anesthetic care unit length of stay

<sup>d</sup> Body Mass Index



**Figure 2.** Kruskal-Wallis test for independent samples, comparing the median length of stay (LOS) measured in minutes (min) in the post-anesthetic care unit (PACU) among different pain severity categories of the Verbal Rating Scale (VRS),  $p < .001$ . \* Dunn's test with  $p < 0.05$  indicated by brackets.

Following an identical pattern, we grouped the totality into BMI categories (as in Table 3) and compared their LOS PACU and linear NRS values for each category. The results in both instances had no significant impact (Kruskal-Wallis;  $p=0.570$  and  $p=0.997$ ) (data not shown).

The ASA and NYHA Classifications are shown in Table 7 with an indication of the patients' presurgical general functional capacity for further characterization of the study group. The former will double as a subgroup partitioning instrument. For ASA, the median of 2 (IQR=1) of physical status in all patients is synonymous with the second class (ASA II), showing an abundance of “mild systemic disease”. Due to its small sample size ASA IV (N=1) was not considered as a subgroup. With a median of 1 (IQR=1) the majority of patients had “no limitation of physical activity”, in accordance with NYHA Class I.

**Table 7.** Descriptive statistics of ordinal variables in total sample (N=283)

| Classification(s)    | Class   | N   | %    | Median (IQR) |
|----------------------|---------|-----|------|--------------|
| ASA PS <sup>a</sup>  | ASA I   | 37  | 13.1 | 2 (1)        |
|                      | ASA II  | 110 | 38.9 |              |
|                      | ASA III | 79  | 27.9 |              |
|                      | ASA IV  | 1   | 0.3  |              |
|                      | ASA V   | -   | -    |              |
|                      | ASA VI  | -   | -    |              |
|                      | Missing | 56  | 19.8 |              |
| NYHA FC <sup>b</sup> | I       | 55  | 19.4 | 1 (1)        |
|                      | II      | 24  | 8.5  |              |
|                      | III     | 3   | 1.1  |              |
|                      | IV      | -   | -    |              |
|                      | Missing | 201 | 71.0 |              |

Data are presented as number of participants (N), as percentage (%) and as median with interquartile range (Median (IQR)). Source of classification (124, 167).

<sup>a</sup> American Society of Anesthesiologists (ASA) Physical Status Classification System

<sup>b</sup> New York Heart Association (NYHA) Functional Classification

Correlation coefficients of relationships between the PACU LOS and either NRS or BMI were calculated in each of the first three ASA classes and summarized in Table 8, as well as visualized in Figure 3. Regarding the association between LOS and NRS we found weak to moderate significant positive correlations in ASA II and III,  $r_s(99) = 0.295$ ,  $p=0.003$  and  $r_s(69) = 0.379$ ,  $p=0.001$ , respectively. The association was less pronounced in ASA I,  $r_s(33) = 0.202$ ,  $p=0.245$ . There was no correlation between time and BMI in any of the ASA groups.

**Table 8.** Rank correlation of outcome measures subcategorized by ASA Classification

| Class                | Variables                                   | N   | Rank correlation coefficients |             |                              |             |
|----------------------|---|-----|-------------------------------|-------------|------------------------------|-------------|
|                      |   |     | Spearman's<br>(rho) $\rho$    | P           | Kendall's<br>(tau) $\tau$ -b | P           |
| ASA <sup>a</sup> I   |   |     |                               |             |                              |             |
|                      | PACU LOS <sup>b</sup> x<br>NRS <sup>c</sup> | 35  | 0.202                         | .245        | 0.139                        | .279        |
|                      | PACU LOS <sup>b</sup> x<br>BMI <sup>d</sup> | 37  | -0.053                        | .753        | -0.045                       | .703        |
| ASA <sup>a</sup> II  |   |     |                               |             |                              |             |
|                      | PACU LOS <sup>b</sup> x<br>NRS <sup>c</sup> | 101 | 0.295                         | <b>.003</b> | 0.216                        | <b>.003</b> |
|                      | PACU LOS <sup>b</sup> x<br>BMI <sup>d</sup> | 107 | 0.013                         | .891        | 0.016                        | .810        |
| ASA <sup>a</sup> III |   |     |                               |             |                              |             |
|                      | PACU LOS <sup>b</sup> x<br>NRS <sup>c</sup> | 71  | 0.379                         | <b>.001</b> | 0.286                        | <b>.001</b> |
|                      | PACU LOS <sup>b</sup> x<br>BMI <sup>d</sup> | 77  | 0.108                         | .350        | 0.078                        | .320        |

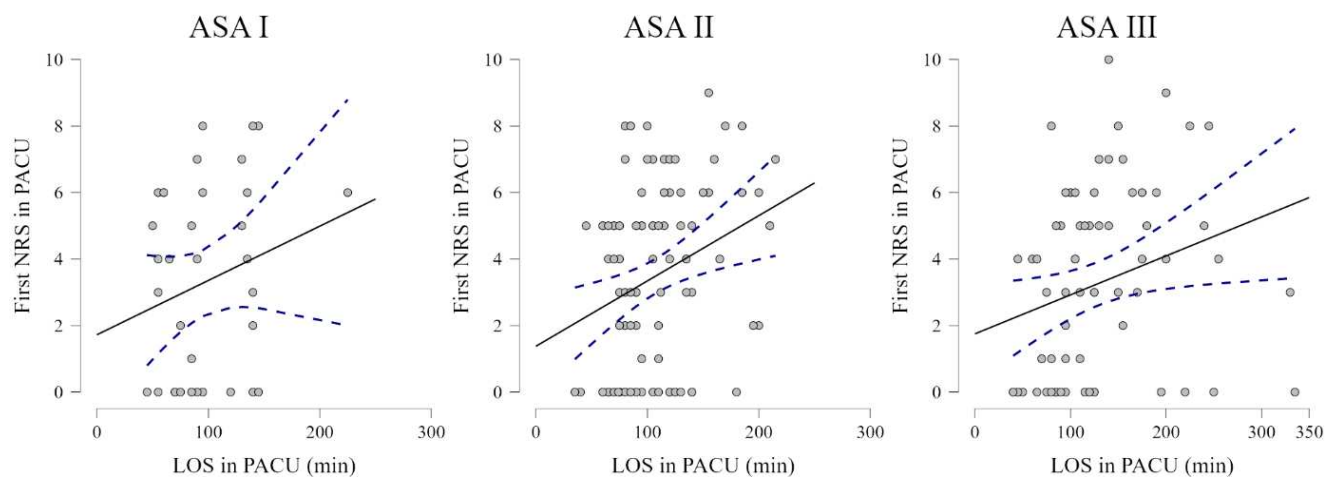
Data are presented as number of participants (N). Significant P-values are bold.

<sup>a</sup> American Society of Anesthesiologists (ASA) Physical Status Classification System

<sup>b</sup> Post-anesthetic care unit length of stay

<sup>c</sup> Numerical Rating Scale

<sup>d</sup> Body Mass Index



**Figure 3.** Descriptive visualization of correlations between the first collected Numeric Rating Scale (NRS) score and length of stay (LOS) in minutes (min) in PACU, sub-grouped in ASA Scores. In ASA I the correlation was not significant ( $p=0.245$ ). For ASA II and III  $p$ -values were, respectively,  $p=0.003$  and  $p=0.001$ .

There was a significant variance in median LOS times between the investigated ASA clusters,  $H(2) = 7.253$ ,  $p = 0.021$ ,  $\eta^2 = 0.026$ , with to ASA I-III congruently increasing medians of 85.0 (IQR=60), 102.5 (IQR=55), and 115.0 (IQR=67.5) minutes (data not shown).

A second division into subgroups was made on the basis of the operations performed in the entire sample, displayed and ordered by the expected painfulness, according to previous literature, in Table 9. Orthopaedic/traumatological surgeries were the most common (N=97), followed by laparoscopic procedures (N=58), and operations on female organs (N=38) among our whole sample. Please take notice that with 17 and 2 participants, respectively, the thoracic surgery and otolaryngology groups did not satisfy the inclusion requirements for statistical tests set by the researches based on sample sizes.

**Table 9.** Subgroups of surgical specialty in decreasing order of painfulness according to Gerbershagen et al. (131) in the total sample (N=283)

| Type of surgical specialty               | N  | %    |
|--|----|------|
| Orthopaedics & traumatology              | 97 | 34.3 |
| General surgery (abdominal, open)        | 20 | 7.1  |
| General surgery (laparoscopic)           | 58 | 20.5 |
| Thoracic surgery                         | 17 | 6.0  |
| Gynecological surgery (incl. mastectomy) | 38 | 13.4 |
| Otolaryngology Surgery                   | 2  | 0.7  |
| General surgery (non-abdominal)          | 21 | 7.4  |
| Urologic surgery                         | 30 | 10.6 |

Data are presented as number of participants (N) and as percentage (%).

Among the most surgical subgroups we were again able to show positive significant correlations between the PACU time and the NRS and, as in the previous tests, no correlation was observed in any group with respect to BMI. The results have been summarized in Table 10. In the first and last group (i.e., predictively most and least ranking of painfulness), weak and high moderate correlation coefficients are seen. Namely the orthopaedic/traumatological surgeries and the urological surgeries, with  $r_s(88) = 0.284$ ,  $p=0.007$  and  $r_s(26) = 0.466$ ,  $p=0.012$ , respectively. Please note the almost significant positive correlation in the fourth-ranked group for painfulness, gynecologic surgeries (N=38) of  $r_s(36) = 0.317$ ,  $p=0.052$ .



**Table 10.** Rank correlation of outcome measures subcategorized by type of surgery

| Specialties                          | Variables                                | N  | Rank correlation coefficients |             |                              |             |
|--------------------------------------|--|----|-------------------------------|-------------|------------------------------|-------------|
|                                      |  |    | Spearman's<br>(rho) $\rho$    | <i>P</i>    | Kendall's<br>(tau) $\tau$ -b | <i>P</i>    |
| Orthopaedics & traumatology          |  |    |                               |             |                              |             |
|                                      | PACU LOS <sup>a</sup> x NRS <sup>b</sup> | 90 | 0.284                         | <b>.007</b> | 0.205                        | <b>.008</b> |
|                                      | PACU LOS <sup>a</sup> x BMI <sup>c</sup> | 94 | 0.167                         | .107        | 0.117                        | .101        |
| General surgery<br>(abdominal, open) |  |    |                               |             |                              |             |
|                                      | PACU LOS <sup>a</sup> x NRS <sup>b</sup> | 18 | 0.179                         | .478        | 0.124                        | .502        |
|                                      | PACU LOS <sup>a</sup> x BMI <sup>c</sup> | 20 | 0.085                         | .721        | 0.043                        | .795        |
| General surgery<br>(laparoscopic)    |  |    |                               |             |                              |             |
|                                      | PACU LOS <sup>a</sup> x NRS <sup>b</sup> | 50 | 0.205                         | .152        | 0.140                        | .182        |
|                                      | PACU LOS <sup>a</sup> x BMI <sup>c</sup> | 58 | 0.015                         | .910        | 0.021                        | .819        |
| Gynecological<br>surgery             |  |    |                               |             |                              |             |
|                                      | PACU LOS <sup>a</sup> x NRS <sup>b</sup> | 38 | 0.317                         | .052        | 0.238                        | .052        |
|                                      | PACU LOS <sup>a</sup> x BMI <sup>c</sup> | 37 | -0.088                        | .607        | -0.059                       | .618        |
| General surgery<br>(non-abdominal)   |  |    |                               |             |                              |             |
|                                      | PACU LOS <sup>a</sup> x NRS <sup>b</sup> | 19 | -                             | -           | -                            | -           |
|                                      | PACU LOS <sup>a</sup> x BMI <sup>c</sup> | 20 | 0.154                         | .518        | 0.065                        | .696        |
| Urologic surgery                     |  |    |                               |             |                              |             |
|                                      | PACU LOS <sup>a</sup> x NRS <sup>b</sup> | 28 | 0.466                         | <b>.012</b> | 0.383                        | <b>.010</b> |
|                                      | PACU LOS <sup>a</sup> x BMI <sup>c</sup> | 29 | -0.082                        | .672        | -0.063                       | .638        |

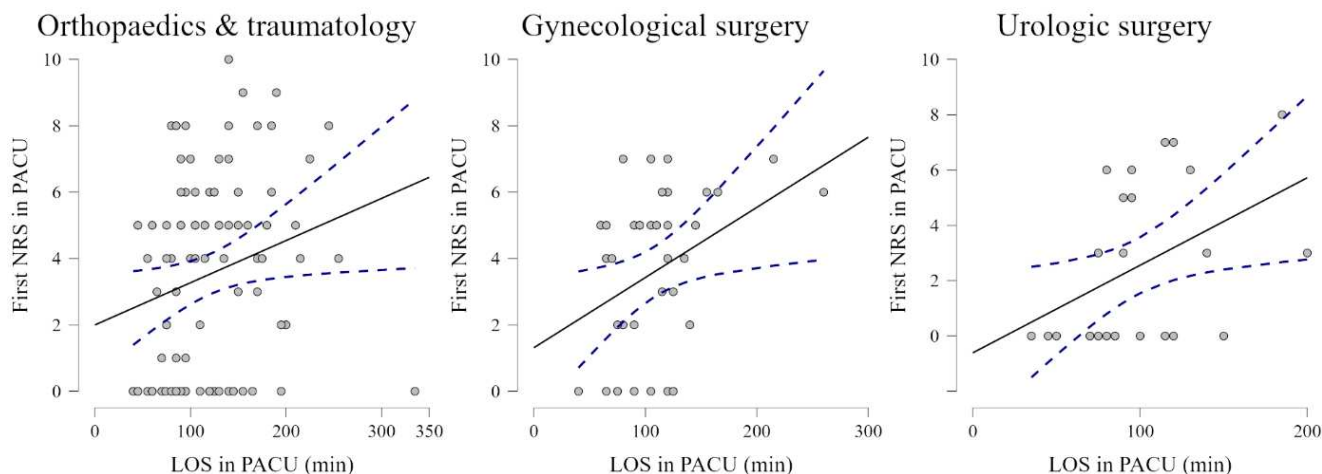
Data are presented as number of participants (N). Significant P-values are bold.

<sup>a</sup> Post-anesthetic care unit length of stay

<sup>b</sup> Numerical Rating Scale

<sup>c</sup> Body Mass Index

The results from Table 10 are visualized in Figure 4 below, showing all three aforementioned categories, in which the outcome variables were almost or complete significantly correlating.



**Figure 4.** Descriptive visualization of correlations between the first collected Numeric Rating Scale (NRS) score and length of stay (LOS) in minutes (min) in PACU, among surgical specialties. Within orthopaedics and urology, they showed significant positive correlation ( $p=0.007$  and  $p=0.0012$ , respectively). In gynecological surgeries the time and NRS correlated positive, but not to a sufficient significance level ( $p=0.052$ ).

For a more thorough investigation we divided the total sample into two additional subgroup sets based on either the mode of anesthesia used or the patient's status as a chronic pain sufferer, both of which can be read from Table 4, and correlation results are shown collectively in Table 11. As for the type of used anesthetic methods, only TIVA and balanced anesthesia could be encompassed due to sufficient sample sizes.

In both forms of anesthesia, the time of stay in PACU correlated positive significant with the first NRS taken from the patient after surgery. The correlation was stronger in the TIVA group than in balanced anesthesia, with  $r_s(27) = 0.462$ ,  $p=0.012$  and  $r_s(226) = 0.269$ ,  $p<.001$ , respectively. For a correlation of PACU LOS with BMI, only in the TIVA group ( $N=31$ ) we saw a weak positive correlation of no statistical significance,  $r_s(29) = 0.159$ ,  $p=0.392$ .

In regard to a previously known medical condition of the patients, we separated the entire data set into two opposing groups (Table 11): 1) with preoperatively chronic pain status ( $N=26$ ) and 2) without this status ( $N=233$ ). Both groups showed a positive correlation of NRS and LOS PACU ( $r_s(24) = 0.262$  and  $r_s(232) = 0.298$ ), but these findings were only significant for the group of “No chronic pain” ( $p=0.195$  vs  $p<.001$ ). No difference was found in the median reported NRS scores ( $p=0.528$ ; Mann-Whitney U) (data not shown). Again, BMI in relation to LOS were without significant results in these subgroups.

**Table 11.** Correlation of outcome values in the sample, split by mode of anesthesia or chronic pain history

| Subgroup           | Variable                                    | N   | Rank correlation coefficients |                  |                              |                  |
|--------------------|---|-----|-------------------------------|------------------|------------------------------|------------------|
|                    |   |     | Spearman's<br>(rho) $\rho$    | <i>P</i>         | Kendall's<br>(tau) $\tau$ -b | <i>P</i>         |
| Mode of Anesthesia |   |     |                               |                  |                              |                  |
| TIVA <sup>a</sup>  | PACU LOS <sup>b</sup> x<br>NRS <sup>c</sup> | 29  | 0.462                         | <b>.012</b>      | 0.333                        | <b>.016</b>      |
|                    | PACU LOS <sup>b</sup> x<br>BMI <sup>d</sup> | 31  | 0.159                         | .392             | 0.093                        | .464             |
| Balanced           | PACU LOS <sup>b</sup> x<br>NRS <sup>c</sup> | 228 | 0.269                         | <b>&lt; .001</b> | 0.199                        | <b>&lt; .001</b> |
|                    | PACU LOS <sup>b</sup> x<br>BMI <sup>d</sup> | 243 | 0.037                         | .564             | 0.026                        | .558             |
| Chronic pain       |   |     |                               |                  |                              |                  |
| Yes                | PACU LOS <sup>b</sup> x<br>NRS <sup>c</sup> | 26  | 0.262                         | .195             | 0.191                        | .203             |
|                    | PACU LOS <sup>b</sup> x<br>BMI <sup>d</sup> | 26  | -0.106                        | .607             | -0.100                       | .480             |
| No                 | PACU LOS <sup>b</sup> x<br>NRS <sup>c</sup> | 233 | 0.298                         | <b>&lt; .001</b> | 0.220                        | <b>&lt; .001</b> |
|                    | PACU LOS <sup>b</sup> x<br>BMI <sup>d</sup> | 251 | 0.046                         | .471             | 0.032                        | .458             |

Data are presented as number of participants (N). Significant P-values are bold.

<sup>a</sup> Total intravenous anesthesia

<sup>b</sup> Post-anesthetic care unit length of stay

<sup>c</sup> Numerical Rating Scale

<sup>d</sup> Body Mass Index

The two modes of anesthesia (TIVA N=31; Balanced N=249), from Table 11 above, differed significant in their median PACU LOS measures of 130.0 (IQR=67.5; TIVA) and 100.0 (IQR=55.0; Balanced) minutes (p=0.01; Mann-Whitney U) (data not shown).

Looking at the complete sample (N=283) again, we found the median LOS in PACU to be 105.0 (IQR=60.0) minutes. Observing the occurrence of PONV, the median time of LOS in PONV-negative patients (N=274) was 100.0 (IQR=58.75) minutes, while the PONV-positive group (N=9) had a median LOS of 140.0 (IQR=65.0) minutes, with a significant difference between both groups (p=.001; Mann-Whitney U). Running the correlation of PACU LOS with the first NRS, as in previous tests, we got a significant positive correlation coefficient of  $r_s(248) = 0.281$ ,  $p < .001$  for the PONV-negative and an insignificant but strong positive correlation in the PONV-positive group  $r_s(7) = 0.637$ ,  $p = 0.065$ . The LOS in regard to BMI in both groups was again without any significant findings (data not shown).

## **5. DISCUSSION**

In this retrospective cross-sectional study, we hypothesized an influence of bodyweight, measured as BMI, or the first postsurgical pain level, indicated by the patients on wakeup in the recovery room, on the length of stay within the post-anesthetic care unit (LOS PACU). For this purpose, we assembled an analyzable dataset from the anesthesia protocols of 283 patients who underwent various forms of surgery with different anesthetic techniques between November 2021 and March 2022 in a single center in Germany.

The results of this study suggest that an increased first stated PACU pain score (i.e., linear NRS) correlates significantly with an increased time spend in the PACU ( $p < 0.001$ ; Table 5). Likewise, a comparison among different levels of pain (i.e., categorical VRS) supports this idea to a significant extent ( $p < 0.001$ ; Table 6). Equally, stratification of the dataset into subgroups, based on widely different characteristics (namely the ASA score, type of operative field or anesthetic method, chronic pain as pre-existing condition, or the occurrence of PONV in PACU), yielded weak to moderate correlations, even though not significant in a few cases, yet all in streamlined manner with positive orientation (i.e., values increased or decreased together). Keep in mind that correlations do not indicate causation, and it is possible that a complicating component, which remained unidentified in our study, may affect both variables in a similar way. However, in the overall view of the results, we reject the null hypothesis that there is no relationship between pain and length of stay in the recovery room, and accept the alternative hypothesis. We interpret these results in continuity with a study conducted by Ganter et al. on more than 12,000 patients, which showed that the level of pain was directly correlated with the LOS in PACU (119). The same study, like the present, discovered a 3% incidence of PONV and an extended LOS in this category (119). Ganter et al. and most of the literature consistently report a predominant risk of PONV in women, which was also reflected in our data, as only women were in the PONV-positive group (119, 168). Moreover, we support, as did Mann-Farrar et al. in this case, their findings that the LOS became longer with increasing ASA class, and in our study the correlation coefficient of NRS to PACU LOS gradually became stronger with successive classes (119, 120). However, it should be noted that Waddle et al. found no significant differences in LOS between ASA classes as early as 1998, in a study of very similar sample size, gender distribution and ASA II weighting as the present (115). We concur with the notion that any factor that can decrease the PACU pain score will also lower the LOS, as Waldron et al. demonstrated that the use of supplementary medications (dexamethasone) lowered postoperative pain scores and patients subsequently had a shorter stay in the PACU (141). In the context of this we, and Nimmaanrat et al. very recently in a study with again similar gender ratio and ASA class II preponderance, reported a direct

association between the PACU pain level upon admission and opioid demand (169). We were also able to demonstrate this to a strong degree ( $p < .001$ ) and would like to elaborate on this finding by noting that there was a positive correlation between opioid demand and LOS ( $p = 0.037$ ). In terms of clinical relevancy, we argue that any measure that can be applied pre- or intraoperative, that will significantly lower the first NRS experienced by the patient in advance, will reduce the time a patient spends in PACU until discharge, together with all consequent advantages like a reduced risk for postoperative chronic pain syndromes and reduced hospital expenses (134). Another such approaches is the highly debated “pre-emptive analgesia” to optimize perioperative pain management, which offers a very logical and interesting deduction by avoiding sensitization and nociception at large, yet has not been able to provide unequivocal results so far (133, 134, 170).

Regarding our second hypothesis, the relationship of BMI to LOS PACU, we did not observe any significant correlations throughout the analysis, and as a matter of fact, we observed inconsistently positive, negative, and zero correlation coefficients among stratified groups. Therefore, we retain the null hypothesis that there is no relationship between BMI and LOS in the recovery room. Although we previously contrasted with the study by Waddle et al., our findings here are in concert with theirs (115). While Gabriel et al. compiled different results, as BMI above 40 prolonged LOS in their study, they explained this by an associated increased risk of postoperative airway obstruction (109). It might be noted here that in our data, only 7.0 percent of patients reached this extreme BMI value, and our sample size might have been underpowered in this regard.

In our study we found further results in addition to the investigated main outcome values, which should be briefly mentioned here. Our sample exhibited parallels to the demographic values found and pointed out in some of the studies mentioned above (115, 169), as well as in the study by Bruins et al., which again showed a very similar male-female ratio in 50,000 PACU patients and ASA II to be the leading fraction (123). This is also true for the ratio of PACU versus OR time, of which the mean in our study as well as in a study by Weissman et al., was 1.5 (122). Looking at the median LOS alone, it was significantly different between the two studied modes of anesthesia ( $p = 0.01$ ), which is similar to the results of Waddle et al. but contradicts the results of van Hemelrijck et al. (115, 171). Nevertheless, both studies examined a greater number of and differently subdivided types, whence our findings are not to be compared. Other studies have already found the types of anesthetic techniques to be important and have incorporated them into prediction models (109, 119). Examining our results for chronic pain patients, we observed a relationship between LOS and NRS, but not a disparity

nor a greater PACU pain score, unlike Cruz et al. demonstrated (105). We would like to emphasize that we do not intend to question this risk factor, but rather to acknowledge it, as it was adequately demonstrated by Cruz et al. and other recent studies (101).

Our study harbors inherently limitations, especially since it is a cross-sectional study, we cannot derive any causal inferences. Another is its retrospective design, as we had to rely on previously collected information recorded by personnel who were probably differently trained and without specific instructions on how to uniformly record the NRS or times, outside of usual teaching that nurses or physicians have. On the contrary, since the data reflects routine clinical reality, this natural heterogeneity can be understood as a strong point. While we were able to show that this sample is fairly comparable to other studies in this research domain, the generalizability may suffer from the fact that the collection was done in only a single center. Perhaps, among other things, for the aforementioned reasons we lack the assumption of normality in our sample and virtually all stratifications, yet we took advantage of this by appropriately using inherently more robust non-parametric statistic tests, with a sacrifice to be generally less powerful and the risk in reducing representation in population.

For future studies to explore that associations in more depth, we recommend a prospective design, the use of a uniformly applied multidimensional pain assessment instrument, consideration of other non-medical confounders (such as transportation, bed or staff availability), and a focus on fewer highly standardized surgical procedures to reduce bias.

In conclusion, we were able to identify a significant positive correlation between the postsurgical pain level and the length of stay in the recovery room, and we are confident that the findings of this study may inspire additional investigations, potentially enhance clinical practice and planning effectiveness (e.g., surgery timetabling and staff deployment), and therefore avoid PACU overloading, improve patient safety, and lower hospital expenditures.

## **6. CONCLUSION**



1. The PACU LOS does significant positive correlated with the postoperative NRS.
2. The median LOS gets longer with each VRS pain category.
3. The correlation is also to be found across different ASA classes, especially significant between ASA II and III.
4. The median LOS gets longer with each ASA class.
5. A significant positive PACU LOS to NRS correlation is apparent in TIVA as well as balanced anesthesia.
6. No correlation was observed between the PACU LOS and BMI.
7. Pain and nociception are of such complex and multidimensional nature, that there is still need for a lot of ambitious small studies to piece together the entire picture.

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## **8. SUMMARY**

**Objectives:** This study primarily aimed to find a relationship between the length of stay until discharge in the post-anesthetic care unit and the BMI of patients, as well as the first postsurgical pain level they expressed after various forms of surgery. Furthermore, we sought to compare these outcome values with various demographic and perioperative data.

**Materials and methods:** A retrospective cross-sectional study design was applied, analyzing the anesthesia record sheets of 283 patients who underwent anesthesia within the scope of their surgery and had a subsequent stay in PACU in a time period from November 2021 to March 2022 in the REGIOMED Hospital Coburg, Germany. As these record sheets were without personal information, the resulting dataset remained anonymous. The randomly drawn sample was stratified into meaningful layers with regard to several clinical features. The data collected was analyzed with JASP (JASP Team (2022). JASP (Version 0.16.3) [Computer software], Amsterdam, Netherlands) and non-parametric Mann-Whitney-U tests, Kruskal-Wallis tests (including *post hoc* Dunn tests), as well as Kendall's Tau-b ( $\tau_b$ ) and Spearman's Rho ( $\rho$ ) correlation tests were applied.

**Results:** The mean age of the sample was  $59.6 \pm 17.6$  years, ranging from 18 to 91 years. The mean BMI was  $28.9 \pm 6.1$  kg/m<sup>2</sup>, the mean NRS was  $3.4 \pm 2.8$ , and the mean LOS was  $114.0 \pm 50.7$  minutes. The majority of the sample was female (57.6%), had a Class II ASA score (39.9%), had no prior history of chronic pain (90.1%), underwent balanced anesthesia (88%), and orthopaedic surgery (34.3%). We found a significant positive correlation between PACU LOS and postsurgical NRS patients expressed in the PACU (Spearman's  $\rho$ ;  $r_s(257) = 0.3$ ,  $p < .001$ ). We discovered a significant difference in median LOS across the four severity groups after categorizing the NRS into VRS labels and applying a Kruskal-Wallis H test ( $H(3) = 20.695$ ,  $p < .001$ ,  $\eta^2 = 0.08$ ). There was a significant difference in median LOS comparing ASA I through III ( $H(2) = 7.253$ ,  $p = 0.021$ ,  $\eta^2 = 0.026$ ). We discovered a positive correlation tendency among all of the five surgical specialties investigated, two of which were significant ( $p = 0.007$ ,  $p = 0.012$ ). BMI and PACU LOS did not significantly correlate throughout the entire sample ( $\rho$ ;  $r_s(275) = 0.03$ ,  $p = 0.642$ ) or when subdivided into any of the subgroups.

**Conclusion:** This study confirmed that a significant positive correlation between the postsurgical pain level and the length of stay in the recovery room exists. In addition, we draw the conclusion that BMI values—high or low—have no influence on LOS.



## **9. CROATIAN SUMMARY**

**Naslov:** Utjecaj boli i tjelesne težine na vrijeme oporavka odraslih pacijenata nakon anesthezijske: retrospektivna presječna studija

**Ciljevi:** Ovo je istraživanje primarno imalo za cilj pronaći odnos između duljine boravka do otpusta u postanestezijskoj jedinici i BMI bolesnika, kao i prve postoperativne razine boli koju su iskazivali nakon različitih oblika kirurškog zahvata. Nadalje, nastojali smo usporediti ove vrijednosti ishoda s različitim demografskim i perioperativnim podacima.

**Materijali i metode:** Primijenjen je retrospektivni dizajn presječne studije, analizirajući anestezijske listove 283 pacijenta koji su bili podvrgnuti anesteziji u okviru svoje operacije i kasnije su boravili u PACU u vremenskom razdoblju od studenog 2021. do ožujka 2022. u bolnici REGIOMED Coburg, Njemačka. Kako su ti zapisnici bili bez osobnih podataka, rezultirajući skup podataka ostao je anonimn. Nasumično izvučeni uzorak stratificiran je u značajne slojeve s obzirom na nekoliko kliničkih značajki. Prikupljeni podaci analizirani su JASP-om (JASP Team (2022). JASP (Version 0.16.3) [Računalni softver], Amsterdam, Nizozemska) i neparametrijskim Mann-Whitney-U testovima, Kruskal-Wallisovim testovima (uključujući *post hoc* Dunnove testove), kao i primijenjeni Kendallov Tau-b ( $\tau_b$ ) i Spearmanov Rho ( $\rho$ ) korelacijski test.

**Rezultati:** Prosječna dob uzorka bila je  $59,6 \pm 17,6$  godina, u rasponu od 18 do 91 godine. Srednji BMI iznosio je  $28,9 \pm 6,1$  kg/m<sup>2</sup>, srednji NRS  $3,4 \pm 2,8$ , a srednji LOS  $114,0 \pm 50,7$  minuta. Većina uzorka bile su žene (57,6%), imale su rezultat klase II ASA (39,9%), nisu imale prethodnu povijest kronične boli (90,1%), podvrgnute su uravnoteženoj anesteziji (88%) i ortopedskoj operaciji (34,3%). Pronašli smo značajnu pozitivnu korelaciju između PACU LOS i postkirurških NRS pacijenata izraženih u PACU (Spearmanov  $\rho$ ;  $r_s(257) = 0,3$ ,  $p < 0,001$ ). Otkrili smo značajnu razliku u medijanu LOS-a u četiri skupine ozbiljnosti nakon kategorizacije NRS-a u VRS oznake i primjene Kruskal-Wallis H testa ( $H(3) = 20,695$ ,  $p < 0,001$ ,  $\eta^2 = 0,08$ ). Postojala je značajna razlika u medijanu LOS-a uspoređujući ASA I do III ( $H(2) = 7,253$ ,  $p = 0,021$ ,  $\eta^2 = 0,026$ ). Otkrili smo pozitivnu tendenciju korelacije između svih pet istraživanih kirurških specijalnosti, od kojih su dvije bile značajne ( $p = 0,007$ ,  $p = 0,012$ ). BMI i PACU LOS nisu značajno korelirali u cijelom uzorku ( $\rho$ ;  $r_s(275) = 0,03$ ,  $p = 0,642$ ) ili kada su podijeljeni u bilo koju od podskupina.

**Zaključak:** Ovo je istraživanje potvrdilo da postoji značajna pozitivna korelacija između razine postoperativne boli i duljine boravka u sobi za oporavak. Osim toga, zaključujemo da vrijednosti BMI-visoke ili niske-nemaju utjecaja na LOS.

## **10. CURRICULUM VITAE**

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2013 – 2015 Paramedic Education DAA-Meiningen, Germany  
2005 – 2013 CVG Caspar-Vischer-Gymnasium Kulmbach, Germany

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2015 – 2016 Paramedic, Lichtenfels, Germany  
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