# Rapid Eye Movement-sleep is reduced in patients with acute uncomplicated diverticulitis - an observational study

Chenxi Huang, Mahdi MA Alamili, Claus Henrik CHN Nielsen, Jacob Rosenberg, Ismail Gögenur

Introduction: Sleep disturbances are commonly found in patients in the postoperative period. Sleep disturbances may give rise to several complications including cardiopulmonary instability, transient cognitive dysfunction and prolonged convalescence. Many factors including host inflammatory responses are believed to cause postoperative sleep disturbances, as inflammatory responses can alter sleep architecture through cytokine-brain interactions. Our aim was to investigate alteration of sleep architecture during acute infection and its relationships to inflammation and clinical symptoms. **Materials & Methods:** In this observational study, we included thirteen patients with acute uncomplicated diverticulitis as a model to investigate the isolated effects of inflammatory responses on sleep. Patients were admitted and treated with antibiotics for two nights, during which study endpoints were measured by polysomnography recordings, self-reported discomfort scores and blood samples of cytokines. One month later, the patients, who now were in complete remission, were readmitted and the endpoints were re-measured (the baseline values).

**Results:** Total sleep time was reduced 4 % and 7 % at both first (p = 0.006) and second (p = 0.014) nights of diverticulitis, compared to baseline. The rapid eye movement sleep was reduced 33 % at first night (p = 0.016), compared to baseline. Moreover, plasma IL-6 levels were correlated to non-rapid eye movement sleep, rapid eye movement sleep and fatigue.

**Conclusion:** Total sleep time and rapid eye movement sleep were reduced during nights with active diverticulitis and correlated with markers of inflammation.

#### 2 Title page

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#### 38 Introduction

Subjective and objective sleep disturbances are commonly found after major surgery (Gogenur et al. 39 2009; Kain & Caldwell-Andrews 2003; Madsen et al. 2013; Rosenberg 2001). Several studies have 40 41 demonstrated reduction or abolishment of slow-wave sleep (SWS) and rapid eye movement (REM) sleep during the first nights of sleep after surgery (Gogenur et al. 2008; Hansen et al. 2013; Krenk et al. 42 2012; Rosenberg et al. 1994). Sleep disturbances may give rise to several complications including 43 44 cardiopulmonary instability, cardiac morbidity, transient cognitive dysfunction, inflammation, prolonged convalescence, fatigue, and hyperalgesia (Chouchou et al. 2014; Cremeans-Smith et al. 45 2006; Krenk et al. 2010; Mullington et al. 2009; Rosenberg 2001). 46 Many factors may influence postoperative sleep: discomfort including pain, use of drugs 47 48 including opioids, nursing environments, psychological factors, effects of general anesthesia, and the surgical trauma itself (Chouchou et al. 2014; Rosenberg 2001). Surgical trauma may lead to activations 49 of metabolic, endocrine and inflammatory responses (Rosenberg-Adamsen et al. 1996), the surgical 50 stress response. Sleep architecture can be altered by certain cytokines (IL-1 $\beta$ , TNF- $\alpha$  and IL-6) that are 51 52 key mediators in the host inflammatory response (Pollmacher et al. 2000). This same universal host inflammatory response is also occurring during infections and after surgical trauma (Rosenberg-53 Adamsen et al. 1996). However, the isolated effect of this inflammatory response on sleep in a clinical 54 55 population without surgery and general anesthesia has never before been investigated. Our hypothesis was therefore that sleep architecture is altered during acute inflammation 56 (diverticulitis), and the changes would correlate to level of circulating inflammatory cytokines. The 57 58 aim of the present study was to report the sleep architecture in the course of acute uncomplicated colonic diverticulitis and investigate the relationship between acute inflammation, sleep disturbances 59 and subjective discomfort. Since postoperative sleep disturbances can lead to complications that 60

complicate the recovery of surgical patients <sup>3,9-12</sup>, identifying key factors that influence postoperative
sleep must be of particular relevance for anesthesiology.

#### 63 Materials & Methods

All patients were enrolled after given written informed consent and the study was approved by the
Ethics Committee of Capital Region of Denmark (ref: H-1-2012-155) and the Danish Data Protection
Agency. The study was registered on www.clinicaltrials.gov (ref: NCT01840852).

We included patients between the age of 18 and 75 years, with The American Society of 67 Anesthesiologists (ASA) Physical Status Classification I-III and with a CT-scan confirming acute 68 uncomplicated diverticulitis (Hansen and Stock stage I) (Klarenbeek et al. 2012). The onset of lower 69 abdominal pain and fever had to be within 72 hours prior to admission. The exclusion criteria were 70 patients with diverticulitis requiring surgical intervention, complicated diverticular disease (fistula or 71 72 abscess), onset of symptoms more than 3 days from inclusion, recent history (up to 3 months) of 73 surgical intervention, myocardial infarction or arrhythmia, autoimmune diseases (Inflammatory bowel disease, lupus, multiple sclerosis), sleep disorders including obstructive sleep apnea, night shift 74 professions, daily use of opioids, psychoactive drugs, or hypnotics, psychiatry disorders, daily 75 76 consumption of more than 50 gram of alcohol, diabetes mellitus, predicted bad compliance (language difficulties, etc.), pregnancy or nursing, urinary or fecal incontinence, severe kidney disease or current 77 78 cancer. Furthermore, sleep quality was screened with Pittsburgh Sleep Quality Index (PSQI) to exclude 79 any poor sleepers (PSQI > 5) (Buysse et al. 1989).

The study was composed of three nights of sleep monitoring in total, all from 2300 hour (h) (lights out) to 0700 h (lights on) in a private room. After two successive nights of sleep monitoring, named as study night 1 (S1) and study night 2 (S2), patients continued their treatment according to standard treatment guidelines for the department. Patients were re-admitted at 30 days after study night

1 to attend the last study night 3 (S3). In case of relapse or failure of treatment during these periods, the patient was excluded. Patients were prohibited from intake of stimulating beverages or alcohol during the day of the study nights. Prior to lights out, light intensity in the room with all light sources off was measured with a luxmeter (Elma 1335 Luxmeter, Elma, Greve, Denmark), and only a level below 10 lux was acceptable. The blood samples were collected at 2230 h followed by administration of selfreported discomfort scales.

Polysomnography was performed with a portable recording unit (Embla titanium, Natus 90 Medical Incorporated, San Carlos, California, USA). Continuous recording from 2300 h to 0700 h was 91 made by using four-channel bipolar electroencephalography, EEG, (C4-M1, C3-M2, O2-M1, O1-M2), 92 93 two-channel electrooculography, EOG, and two-channel electromyography (submental). Reusable 10 mm gold cup electrodes (Natus Medical Incorporated, San Carlos, California, USA) were applied for 94 EEG, and single use self-adhesive electrodes were applied for EOG and EMG (Ambu® Neuroline 720, 95 96 Ballerup, Copenhagen, Denmark). All electrodes were placed in accordance to The American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events 2007 97 and the skin was prepared with light abrasion and alcohol swaps before electrode fixation. Sleep 98 staging was performed in accordance to The AASM Manual for the Scoring of Sleep and Associated 99 Events 2007. Staging was performed by one experienced, trained scorer blinded to study nights using 100 the software Remlogic 3.2 (Natus Medical Incorporated, San Carlos, California, USA). Sleep 101 recordings were staged in epochs of 30 seconds as either N1 (stage 1 sleep), N2 (stage 2 sleep), N3 102 (stage 3 sleep), REM (REM sleep) or W (awake). All other sleep parameters were calculated on the 103 104 basis of these sleep stages. Total sleep time (TST) summed up the time spent across all sleep stages, while sleep onset (SO) summed up the time spent in wake stage before the first sleep stage. Wake after 105 sleep onset (WASO) summed up the time spent awake after sleep onset and before final awakening. 106 107 Lastly, number of awakening (NOA) showed the number awakening from any sleep stages.

108 Subjective measures concerning discomfort were administered 10 minutes before lights out, including 100-mm visual analogue scale (VAS) of pain at rest and pain during movements (0 mm no 109 pain and 100 mm worst pain imaginable), a 9-point Karolinska Sleepiness Scale (KSS) ranging from 110 extremely alert (equals score 1) to fighting sleep (equals score 9) (Akerstedt & Gillberg 1990). Fatigue 111 and malaise were measured in VAS of overall fatigue (0 mm = no sense of fatigue and 100 = worst 112 fatigue imaginable) and general well-being (0 mm = extremely well and 100 = extreme malaise), 113 respectively. Lastly, a 100-mm VAS of poor sleep quality (0 mm best sleep and 100 mm worst sleep 114 imaginable) was also administered in the following morning to assess self-reported sleep quality. 115 At 2230 h the blood samples were taken. The plasma was extracted and then stored at - 80 116 117 degree Celsius until analysis. Tumor necrosis factor alpha (TNF- $\alpha$ ), interleukin-1 beta (IL-1 $\beta$ ), interleukin-2 (IL-2), interleukin-6 (IL-6), and interleukin-10 (IL-10) were measured in a Luminex 100 118 IS analyzer (Luminex Corporation, Austin, TX, USA) using appropriate multiplex antibody bead kits 119 120 purchased from Invitrogen (Invitrogen Corporation, Carlsbad, CA, USA). Data were analyzed using StarStation version 2.0 software (Applied Cytometry Systems, Sheffield, UK). The lower levels of 121 detection were as followed (in picogram / milliliter): TNF-α: 0.7, IL-1β: 0.4, IL-2: 2.8 IL-6: 0.2, IL-10: 122 0.4. 123

REM sleep time was the primary endpoint of this study, while the secondary endpoints 124 included other sleep data, scores of self-reported discomfort and levels of circulating cytokines. We 125 assumed that REM sleep duration was approximately 70 minutes for healthy subjects between the ages 126 of 40 to 50 with a standard deviation of 30 minutes (Ohayon et al. 2004). A 25% reduction of REM 127 sleep between study nights 1 and 3 was considered as of clinical importance. It was estimated that 11 128 patients were needed, when a two-sided significance level of 5% and a power of 0.90 were applied. 129 Wilcoxon's signed-rank test was used for all data (sleep data, self-reported discomfort scores and 130 131 cytokine levels) as paired analyses between S1 and S3, and S2 and S3. Spearman's correlation was

used to analyze the correlations between changes in sleep stages (as per cent of total sleep time) and
changes in cytokine levels from S1 to S3 and from S2 to S3. The correlations estimated were the
differences, rather than the absolute values, between these measurements. The correlations were also
calculated between changes in self-reported discomfort scores and changes in sleep stages, as well as
changes in cytokine levels and changes in self-reported discomfort scores. All data were presented as
median and ranges or quartiles. IBM SPSS Statistics for Windows, Version 20.0 (Armonk, NY: IBM
Corp.) was used to carry out the calculations. The level of statistical significance was set to 0.05.

#### 139 **Results**

Thirteen patients were enrolled, 11 completed the study, and two were excluded, one due to recurrence of diverticulitis, and one due to technical failure of the PSG recordings. Characteristics of patients, diverticular disease and analgesics consumption are presented in table 1. All 11 patients were treated with oral or intravenous antibiotics according to standard routines and oral paracetamol, if required also ibuprofen, during their admission.

All sleep data are presented in table 2. TST values were significantly reduced from both S1 and S2 to S3, whereas wake time and wake time after sleep onset (WASO) were significantly increased. REM sleep was significantly decreased at S1 compared with S3. There was no statistical difference in number of awakenings between the study nights. Due to the risk of first night effect, post hoc paired analysis of TST, wake time and WASO between S1 and S2 were performed and showed no differences (W: p = 0.859, TST: p = 0.859, WASO: p = 0.533).

151 Cytokine levels are depicted in figure 1. Vast majority of IL-1 $\beta$  and IL-2 measurements were 152 found below the detection thresholds, therefore they were excluded from further analysis. IL-6 levels 153 were increased from both S1 and S2 to S3 (p = 0.008 and p = 0.051 respectively). IL-10 (p = 0.128 for

both nights versus S3) and TNF- $\alpha$  (p = 0.103 for S1, p = 0.314 for S2), levels were decreased over study nights, however without statistical significance.

Subjective discomfort scores are depicted in figure 2. Malaise (p = 0.003, p = 0.005), pain during movements (p = 0.005, p = 0.005), resting pain (p = 0.003, p = 0.008) and poor sleep quality (p = 0.003, p = 0.041) were significantly diminished at S1 and S2 compared with S3. The fatigue was also diminished, however only with statistical significance from S1 to S3 (p = 0.006), but not from S2 to S3 (p = 0.374). Lastly, no significant differences were found for sleepiness for both nights (p = 0.892, p = 0.619 respectively).

Since the vast majority of IL-1 $\beta$  and IL-2 measurements were below the detection limits, they 162 163 were excluded from correlation analyses. The correlations between cytokine levels and sleep stages are stated in table 3. We found significant associations in changes in IL-6 levels and changes in sleep 164 stages as percentage of TST from both S1 and S2 to S3. There were strong correlations between IL-6 165 and REM (S1: r = -0.68, p = 0.02 and S2: r = -0.67, p = 0.03) and NREM (S1: r = 0.68, p = 0.02 and 166 S2: r = 0.67, p = 0.03). In addition, a moderate correlation between IL-6 and N2 (S1: r = 0.60, p = 0.05167 and S2: r = 0.63, p = 0.04) was found. We did not find any significant correlations between changes in 168 self-reported discomfort and changes in sleep stages; however, we did find a positive correlation 169 between changes in fatigue and IL-6 levels from S1 to S3 (r = 0.61, p = 0.05). No other significant 170 associations were found between changes in discomfort and changes in cytokine levels. 171

#### 172 Discussion

173 We used acute uncomplicated diverticulitis as a model to investigate the effects of inflammatory

174 responses on sleep and found that TST was consistently reduced at both study nights with diverticulitis

175 (S1 and S2) due to increased W and WASO, and that REM sleep was decreased at S1. We also found

that subjective discomfort scores were increased except sleepiness at both diverticulitis nights. Lastly,

we found a significant increase in IL-6 levels during the study nights during which the patients had
diverticulitis, and this increase was correlated to changes in NREM sleep (including N2 sleep), REM
sleep, and fatigue scores.

Suppression of REM sleep and promotion of WASO and NREM sleep found in this study are 180 similar to findings observed in clinical polysomnography studies of patients with infections such as 181 early stage HIV infection and acute rhinovirus infection (Opp 2009). In addition, sleep studies using 182 endotoxin have been performed in healthy humans (Pollmacher et al. 2000), showing increased wake 183 time, NREM sleep and decreased REM sleep after endotoxin administration (Mullington et al. 2000; 184 Trachsel et al. 1994). In addition, the endotoxin-induced IL-6 elevation was positively correlated with 185 186 REM latency, N2 sleep and wake time, and negatively correlated with REM sleep (Pollmacher et al. 1993). The reducing effect of REM sleep on IL-6 levels has also been demonstrated in another study 187 (Spath-Schwalbe et al. 1998). One cross-sectional study has showed that levels of circulating IL-6 188 189 within normal ranges are significantly correlated to sleep architecture (increase of REM latency and WASO) when demographical variations were controlled (Hong et al. 2005). These findings are 190 consistent with the associations we found in the present study, and further support the growing 191 evidences of the sleep regulating roles of pro-inflammatory cytokines (Bryant et al. 2004). So far, 192 evidence suggests that IL-6 can act directly on the central nervous system (Imeri & Opp 2009), 193 including activation of the hypothalamic-pituitary-adrenal axis (HPA-axis), to exert its effect on sleep 194 regulation (Gomez-Gonzalez et al. 2012). Furthermore, studies have shown that inhibition of the IL-6 195 receptor by tocilizumab can alleviate sleep disturbances and fatigue in patients with rheumatoid 196 197 arthritis (Rohleder et al. 2012; Thomas et al. 2011).

The elevated levels of plasma IL-6 found in the current study are coherent with findings in
recent clinical studies investigating IL-6 levels during the course of acute diverticulitis and other
abdominal infections (Elsing et al. 2012; Rivera-Chavez et al. 2003). However, IL-1β and IL-2 levels

201 were not elevated /detectable at all. This discrepancy has previously been observed in patients with 202 acute pancreatitis and appendicitis (Brivet et al. 1999; Rivera-Chavez et al. 2003). It is possible in the current study that levels of IL-1ß and IL-2 may have peaked before the blood sampling, and the 203 cytokines were already bound by high level of endogenous soluble receptors (Brivet et al. 1999). 204 Compared to postoperative sleep disturbances (Rosenberg 2001), REM sleep suppression 205 found in our study was less prominent (33%). SWS and REM sleep are most often absent (100% 206 reduction) during the first nights after major non-cardiac surgery (Rosenberg 2001). In the 207 postoperative period, pain and disturbing hospital environment (noise and staffs) are likely to cause 208 awakenings during the night (Rosenberg 2001), while opioids for pain relief can reduce SWS and REM 209 210 sleep (Shaw et al. 2005). In recent years, more major surgeries have been performed with fast track regimes, in which perioperative care has been optimized with multimodal opioid-sparing analgesia and 211 212 early hospital discharge (home environment) (Kehlet 2008). Despite these efforts, REM sleep in the first postoperative night is still greatly reduced (62 - 92%) (Dette et al. 2013; Hansen et al. 2013; 213 Krenk et al. 2012). One randomized trial also demonstrated that even when opioids were avoided and 214 pain was well managed, REM sleep was still abolished after major surgery (Cronin et al. 2001). In 215 contrast, minor or less invasive surgery, such as laparoscopic surgery, only causes transient SWS 216 reduction (46%), leaving REM sleep unaffected (Rosenberg 2001). These findings may indicate that 217 the magnitude of the surgical trauma, including the inflammatory response, plays a greater role in the 218 postoperative sleep disturbances, compared to pain and opioid usage. Laparoscopic procedures cause 219 less trauma and inflammatory response, manifested by CRP, IL-6 and TNF-α compared to major 220 surgery (Akhtar et al. 1998; Braga et al. 2002), and therefore only causing a transient shift from SWS 221 sleep to shallow NREM sleep. 222

223 Our study has some limitations. Patients were only mildly affected by their disease, and the 224 magnitude of inflammation was therefore low, yet enough eliciting elevation of cytokines, C-reactive

225 protein and body temperature. In our institution, these cases were treated with antibiotics and 226 paracetamol, and to our knowledge, these drugs will not cause any (REM) sleep alteration. Due to the nature of the acute diverticulitis, the investigated periods (S1 and S2) of host inflammatory response 227 were most likely not exactly synchronized amongst the patients. We did, however, only include 228 patients with pain onset less than 72 hours prior to the admission and inflammation in the diverticula 229 proven by CT-imaging and elevated C-reactive protein. Therefore, the inflammatory response was 230 present during the first study night, but the magnitude of this response could still vary between the 231 patients and so could their recovery rate due to the disease states and age differences (Ottinger et al. 232 2014). These uncertainties were attempted to be dealt with using paired observations, where each 233 234 patient was its own control, thus allowing for differences in baseline values between the patients. First night effect refers to reduction of TST and increase of wake time and WASO due to 235 exposure to unfamiliar sleep environment (Toussaint et al. 1995). We did not find any significant 236 237 changes in these sleep parameters between S1 and S2.

#### 238 Conclusion

In conclusion, we found substantial sleep disturbances and subjective complaints in relation to acute
 uncomplicated diverticulitis. Inflammatory parameters correlated to sleep stages and subjective

241 complaints.

242

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### 245 **References**

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### 349 Tables

350 Table 1 Characteristics of patients with acute diverticulitis and their analgesics consumption.

	Subject characteristics	Median	Range
2	Sex (male/female), n	5/6	
	Age (years)	52	(20-74)
3	ASA (I/II/III), n	11/0/0	
	Body Mass Index (BMI)	28	(20-39)
94	Pittsburgh Sleep Quality Index (PSQI)	4	(2-5)
5	Disease characteristics		
	Pain debut (hours)	48	(24-72)
6	Temperature at admission (°C)	37.8	(36.9-39.1)
	Hansen and Stock stage* (0/I/II/III), n	0/11/0/0	
57	Cancer found with endoscopy 30 days after admission, n	0	
8	C-reactive protein level at admission (mg/l)	94	(33-190)
	Analgesics administered		
-9	Paracetamol, n	11	
0	Ibuprofen, n	2	
0	Morphine, n	0	

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Values are median and range. \*Hansen and Stock staging of diverticulitis is a clinical classification that
also accounting for asymptomatic diverticulosis (stage 0) (Klarenbeek et al. 2012). Stages I to III refer
to increasing severity of diverticulitis. Stage I refers to acute uncomplicated diverticulitis, stage II
refers to acute complicated diverticulitis and stage III refers to chronic recurrent diverticulitis. ASA,
American Society of Anesthesiologists.

	Study night 1			Study r	night 2	Study night 3		
	median		p - value	median		p - value	median	
N1 (min)	28	(24-40)	0.169	39	(32-51)	0.722	40	(32-52)
N2 (min)	185	(122-199)	0.477	147	(138-161)	0.424	165	(146-191)
N3 (min)	88	(73-102)	0.423	83	(50-103)	0.477	87	(74-101)
Non REM (min)	285	(242-317)	0.091	284	(264-290)	0.062	293	(286-323)
REM (min)	60	(42-84)	0.016	73	(47-92)	0.068	90	(76-112)
W (min)	119	(92-184)	0.006	106	(94-155)	0.014	89	(61-109)
Sleep onset (min)	39	(26-47)	0.248	26	(19-34)	0.594	29	(15-52)
WASO (min)	78	(55-142)	0.005	86	(68-120)	0.003	50	(28-68)
Awakening (number)	19	(17-27)	0.266	24	(23-29)	0.305	26	(19-31)
TST (min)	361	(297-388)	0.006	374	(326-386)	0.014	391	(371-419)
N1 of TST (%)	9.9	(6.0-12.5)	0.858	11.5	(8.5-14.1)	0.514	9.3	(7.7-14.5)
N2 of TST (%)	47.4	(39.5-54.1)	0.398	45.3	(37.1-52.8)	0.449	42.8	(38.8-45.5
N3 of TST (%)	22.1	(19.5-27.5)	0.929	23.8	(18.5-26.8)	0.610	21.9	(19.5-26.1
NREM of TST (%)	82.5	(76.5-87.5)	0.032	80.6	(75.5-86.5)	0.139	75.5	(72.5-78.0
REM of TST (%)	17.5	(12.5-23.5)	0.036	19.4	(13.5-24.5)	0.139	24.5	(22.0-27.6

368 Table 2 Sleep parameters of patients with acute diverticulitis both during nights of the disease and369 during remission night.

380

381 Values are median and interquartile ranges in the brackets. P-values for Wilcoxon's signed rank test for

382 study nights during diverticulitis compared to remission night (study night 3). Nx, stage x sleep; REM,

rapid eye movement sleep; W, wake time; WASO, wake after sleep onset; TST, total sleep time.

385												
			<b>↑non REM</b>		↑REM	<b>↑N1</b>			<b>↑N2</b>		<b>↑N3</b>	
386			night	night	night	night	night	night	night	night	night	night
			1	2	l	2	l	2	1	2	1	2
387	<b>↑IL-6</b>	correlation	0.68	0.67	-0.68	-0.67	-0.18	-0.48	0.60	0.63	-0.24	-0.18
		p-value	0.02	0.03	0.02	0.03	0.60	0.14	0.05	0.04	0.47	0.61
388	<b>↑IL-10</b>	correlation	0.04	0.36	-0.04	-0.36	0.24	0.17	-0.21	0.12	0.22	-0.03
		p-value	0.91	0.28	0.91	0.28	0.48	0.62	0.53	0.72	0.51	0.93
389	↑TNF-α	correlation	-0.26	0.13	0.26	-0.13	-0.04	0.40	-0.18	0.03	0.30	-0.08
		p-value	0.43	0.71	0.43	0.71	0.90	0.22	0.59	0.93	0.38	0.83

**Table 3** Correlation cross table for changes in sleep stages and cytokine levels.

390 The changes for study night 1 were defined as values of study night 1 minus study night 3 (remission

night), and for study night 2 it was values of study night 2 minus study night 3. Significant correlations

are presented in bold. Values are correlation coefficient and the corresponding p-value. REM, rapid eye

393 movement sleep; Nx, stage x sleep; IL-x, interleukin; TNF, tumor necrosis factor.

#### 395 Figures

**Figure 1** Plasma concentrations of cytokines in patients with acute diverticulitis both during nights of

397 the disease and during remission night.



398

Significant differences between the nights of the disease and remission night were calculated using Wilcoxon's signed rank test and are indicated with \*; p < 0.05, \*\*; p < 0.01. The horizontal broken lines indicate the detection thresholds for the individual cytokines. The whiskers depict interquartile range. The cytokines measured include: IL-10, interleukin 10; IL-6, interleukin 6; TNF- $\alpha$ , tumor necrosis factor alpha.

Figure 2 Subjective discomfort scores in patients with acute diverticulitis both during nights of the
disease and during remission night.



407

408 Significant differences between the nights of the disease and remission night were calculated using 409 Wilcoxon's signed rank test and are indicated with \*; p < 0.05, \*\*; p < 0.01. The whiskers depict 410 interquartile range. Apart from sleepiness, which was measured with KSS, Karolinska Sleepiness

411 Scale; remaining discomfort domains were measured with VAS, visual analogue scale.