

# Improved urinary melatonin level as the perspective indicator that leads to better sleeping quality in bladder cancer patients

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## Abstract

**Background:** Individuals with higher-than-average melatonin concentrations are less likely to develop cancer. In cancer patients, psychosomatic coping patterns and treatment side effects are important indicators of cancer prevention and immune system deterioration. This study focused on changes in the urinary melatonin concentration, life resilience, and sleep quality in bladder cancer patients before, and 3 months after, treatment.

**Methods:** A controlled before-and-after study was performed. The subjects were patients who were previously diagnosed with bladder cancer and had received treatment (transurethral resection of bladder tumor + intravesical chemotherapy). Data from 23 subjects were analyzed.

**Results:** The results showed a significant difference in the melatonin concentration before and after treatment (Wilcoxon signed-rank test,  $Z = -2.220$ ,  $p = 0.026$ ). The melatonin concentration in 16 patients (70%) increased after treatment. The mean Pittsburgh Sleep Quality Index (PSQI) score before treatment was 7.348 (SD = 4.030), which was associated with poor sleep quality. The mean PSQI score after treatment was 6.435 (SD = 3.300;  $Z = -2.071$ ;  $p = 0.038$ ). These results represent the improved sleep quality in patients post-treatment.

**Conclusions:** After treatment, the urinary melatonin concentration and sleep quality (PSQI) improved, both of which were statistically significant in bladder cancer patients. Consequently, bladder cancer treatment should be initiated as soon as possible. There was no significant difference in overall life resilience before and after treatment, possibly because elderly individuals have strong personality traits and emotional stability and are not easily affected by life events or stress.

**Keywords:** bladder cancer, life resilience, sleep quality, transurethral resection of bladder tumor (TURBT), urinary melatonin concentration

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## Introduction

As a common malignant tumor, bladder cancer can be diagnosed in asymptomatic patients when systematic cystoscopies are performed often (i.e. surveillance of non-muscle invasive bladder cancer). Although its incidence and mortality rates are both lower than those of prostate cancer, it is

one of the most expensive cancers to treat.<sup>1–3</sup> According to 2018 global cancer statistics, bladder cancer is the 10th most common cancer worldwide, with approximately 549,000 new cases and 200,000 deaths reported annually. It is more common among males than females, with a fourfold higher incidence in males, worldwide.<sup>4</sup>

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The incidence and mortality rates of bladder cancer have remained the same for many years, and there has been no significant increase in the 5-year survival rate. Among the possible etiological causes, smoking is the most important risk factor for bladder cancer other than occupational exposure to chemical dyes and water pollutants.<sup>4</sup> Long-term exposure to outdoor air pollution is also positively correlated with an increased risk of bladder cancer incidence and death.<sup>5,6</sup> Bladder cancer is the fourth most deadly cancer, ranking only after pancreatic cancer, lung cancer, and liver cancer.<sup>7</sup> In a survey of more than 40,000 cancer patients, among all cancers of the urinary system, bladder cancer is associated with the lowest satisfaction in treatment and care.<sup>8</sup> Therefore, the physical and psychological care and study of bladder cancer patients during their treatment and care are very important.

Most studies have shown that melatonin, which is produced by the pineal gland, has many benefits. For example, it acts as an 'antioxidant' that inhibits certain cancer cells, boosts immune function, improves depression, helps induce sleep, and regulates sleep disorders caused by shift work or jet lag.<sup>1,9-11</sup> The main metabolite of urinary melatonin is 6-sulfatoxymelatonin,<sup>12</sup> which is closely associated with levels measured among patients with endocrine-related cancers. Decreased melatonin secretion at night may lead to decreased immunity and poor sleep quality.<sup>12,13</sup> Moreover, a lower level of melatonin tends to increase the risk of breast or endometrial cancer.<sup>14</sup> A recent study reported that melatonin significantly suppressed the proliferation and signal transduction of bladder cancer cells, and decreased tumor growth and metastasis *in vivo*, thus potentially being beneficial to bladder cancer patients.<sup>1</sup>

Sleep is a natural and recurring biological phenomenon that can meet the physiological and psychological needs of humans. However, a few hours of sleep or a high frequency of sleep disruptions can result in severe sleep disorders.<sup>15</sup> Through proactive treatment, emotional dysfunction, and reduced activity and social function caused by physiological pain and burden can be alleviated for bladder cancer patients.<sup>16</sup> Hence, medical and nursing staff should not ignore these factors that need paying close attention to.

Suffering from illness is an adversity in life, and ill patients will have physical and mental distress symptoms. Having good resilience and exhibiting

positive psychological adaptability in adversity is helpful for maintaining or restoring mental health and improving quality of life.<sup>17,18</sup> Therefore, the purpose of treatment is not simply to alleviate physical and mental symptoms, but prevent recurrence or metastasis. Improved life resilience and enhanced sleep quality after cancer diagnosis and treatment have been regarded as important prognostic management indicators which can help to guide disease treatment and care. Therefore, the purpose of this study was to compare the quality of sleep before and after transurethral resection of bladder tumor (TURBT) of bladder cancer patients.

## Methods

### *Study design and data collection*

This study follows a controlled before-and-after research design. To understand changes in the urinary melatonin concentration, life resilience, and sleep quality in bladder cancer patients before and 3 months after treatment, data were collected on two separate occasions. The first round of data collection was conducted when the patients were initially diagnosed and admitted for treatment; the second data collection was performed at the follow-up visit, 3 months after treatment. The data collected included demographic data, disease characteristics, biochemical test data, the severity of physical symptoms, urinalysis before treatment, and questionnaires concerning life resilience and sleep quality. The contents of the second data collection were similar to those of the first round except the treatment method was added.

### *Study site and participants*

Residents living in the southwestern coastal region of Taiwan had long consumed groundwater with a high arsenic concentration. Therefore, we chose to carry out the current study in the urology unit of a regional hospital in southwest Taiwan. The inclusion criteria included the following: (a) patients who were older than 20 years of age; (b) patients who were initially diagnosed with bladder cancer and were aware of their condition; and (c) patients who demonstrated a clear mental status and were able to communicate verbally. Data from a total of 67 patients were collected, of whom only 23 completed the two questionnaires before and after treatment, as well as the urinalysis. Finally, the data from the 23 patients were analyzed, and the number of valid cases accounted for 34.3%.

### Research instrument

The measurement tools used in this study included questionnaires and laboratory determination of the urinary melatonin concentration. The questionnaire survey included basic demographic data, disease characteristics, the Chinese version of the Life Resilience Index, and the Pittsburgh Sleep Quality Index (PSQI-Chinese version). The Chinese version of the Life Resilience Index contains 29 items with a 7-point Likert scale. The higher the total score is, the better the resilience.

The PSQI was used as the basis for sleep quality assessment. There were a total of 19 questions composed of seven factors, namely, sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medications, and daytime dysfunction. The global scores range from 0 to 21; a score of 5 was used as the cut-off point, with a PSQI  $\leq 5$  indicating good sleep quality.<sup>19</sup>

Regarding melatonin concentration determination, 30 ml urine samples from each patient before and after treatment were collected and freeze-stored at  $-20^{\circ}\text{C}$ . The measurement of 6-sulfatoxymelatonin in urine samples was carried out using a melatonin-sulfate urine enzyme-linked immunosorbent assay (ELISA) kit. The urine sample was thawed, and 1 ml of the sample was pipetted and transferred to a centrifuge tube (Eppendorf). After centrifugation at 3000 rpm for 10 min, the supernatant was removed and repacked for later use. Laboratory assay steps were performed with the IBL International GmbH® melatonin-sulfate urine ELISA Kit (RE54031) in accordance with the manufacturer's instructions (<https://www.ibl-international.com/en/>). The procedures employed are described briefly as: a 10  $\mu\text{l}$  urine sample (control, patient's, or standard) was diluted 50 $\times$  with a trisaminomethane buffer and pipetted into microtiter plate wells. To each well, freshly prepared enzyme-conjugated melatonin and a melatonin-sulfate antiserum (50  $\mu\text{l}$  each) were added. The plate was incubated at room temperature (r.t.) for 2 hrs. The solution was then discarded, and the plate washed four times with 250  $\mu\text{l}$  of a diluted wash buffer. TMB substrate solution (100  $\mu\text{l}$ ) was added to each well and the plate incubated at room temperature for 30 min at r.t., followed by 100  $\mu\text{l}$  of a TMB stop solution. The optical density was measured at 450 nm in a photometer. Detailed protocol could be found from the vendor's website.

### Data analyses

The SPSS 22.0 software package (IBM, USA) was used for data archiving and analysis. The descriptive statistics included the count, percent, frequency, mean, standard deviation (SD), and median. It was not suitable to use the central limit theorem because the sample size was less than 30. Instead, inferential statistics were analyzed using the nonparametric Wilcoxon signed-rank test. Statistical significance was considered when  $p < 0.05$ .

### Results

The results showed that among the 23 patients, there were 15 males (65%) and 8 females (35%) aged 39–83 years, with an average age of 66 years. Among them, there were only 4 patients (17.4%) aged 39–60 years and 19 patients (82.6%) aged 61–83 years. The average sleep time was 6.63 h (SD = 1.67) before treatment and 6.87 h (SD = 1.51) after treatment, and the difference was not statistically significant (Table 1). Analysis of the categorical variables of sleep quality revealed that within 1 month prior to treatment, 34.8% of patients were unable to fall asleep within 30 min more than three times, whereas after treatment, only 17.4% were unable to fall asleep within 30 min more than three times. A total of 62% of the patients reported waking up at night or in the early morning more than three times per month, of which 82.6% woke before treatment and only 4.3% woke after treatment.

A global PSQI score  $\leq 5$  indicates good sleep quality. Among the 23 bladder cancer patients in this study, the mean PSQI score before treatment was 7.348 (SD = 4.029), with a median score of 7 points. Among these patients, 10 (43.5%) had a PSQI  $\leq 5$ . After treatment, the mean PSQI score was 6.435 (SD = 3.300), with a median score of 6 points. Among these patients, 11 (47.8%) had a PSQI  $\leq 5$ . The results from the Wilcoxon signed-rank test revealed 14 negative ranks, 7 positive ranks, and 2 ties in the PSQI post-test minus pretest, indicating that 14 post-test data scores were less than those of the pretest, 7 were greater than those of the pretest, and 2 were the same before and after the test. There was a significant difference in the median pretest and post-test values ( $Z = -2.071$ ,  $p = 0.038$ ), and the PSQI score was significantly decreased in patients with bladder cancer after treatment (Table 2).

Regarding the urinary melatonin concentration, the  $Z$  score of  $-2.220$  ( $p = 0.026$ ) from the

**Table 1.** Characteristics and variables of the study patients (n = 23).

Characteristics	n	Frequency (%)	Variables	Mean	SD
Sex			Average sleep time		
Male	15	65.2	Pre-treatment	6.63	1.67
Female	8	34.8	Post-treatment	6.87	1.51
Age (years)			PSQI Score		
39–60	4	17.4	Pre-treatment	7.348	4.029
61–83	19	82.6	Post-treatment	6.435	3.300
Smoking status			Melatonin concentration		
Yes	8	34.8	Pre-treatment	12.196	20.826
No	15	65.2	Post-treatment	16.323	23.367
			Life Resilience Index		
			Pre-treatment	5.312	0.859
			Post-treatment	5.228	0.872
PSQI, Pittsburgh Sleep Quality Index; SD, standard deviation.					

**Table 2.** The outcome of Wilcoxon signed-rank test.

Outcome variable	Ranks	n	Mean rank	Sum of ranks	Z score	p value
PSQI_post PSQI_pre	Negative	14 <sup>a</sup>	12.43	174.00	-2.071*	0.038
	Positive	7 <sup>b</sup>	8.14	57.00		
	Ties	2 <sup>c</sup>				
	Total	23				
Melatonin_post Melatonin_pre	Negative	7 <sup>d</sup>	9.29	65.00	-2.220*	0.026
	Positive	16 <sup>e</sup>	13.19	211.00		
	Ties	0 <sup>f</sup>				
	Total	23				
Life resilience_post Life resilience_pre	Negative	12 <sup>g</sup>	10.63	127.50	-0.418	0.676
	Positive	9 <sup>h</sup>	11.50	103.50		
	Ties	2 <sup>i</sup>				
	Total	23				

<sup>a</sup>PSQI\_post < PSQI\_pre.  
<sup>b</sup>PSQI\_post > PSQI\_pre.  
<sup>c</sup>PSQI\_post = PSQI\_pre.  
<sup>d</sup>Melatonin\_post < melatonin\_pre.  
<sup>e</sup>Melatonin\_post > melatonin\_pre.  
<sup>f</sup>Melatonin\_post = melatonin\_pre.  
<sup>g</sup>Life resilience\_post < life resilience\_pre.  
<sup>h</sup>Life resilience\_post > life resilience\_pre.  
<sup>i</sup>Life resilience\_post = life resilience\_pre.  
 \*p < 0.05.  
 PSQI, Pittsburgh Sleep Quality Index.

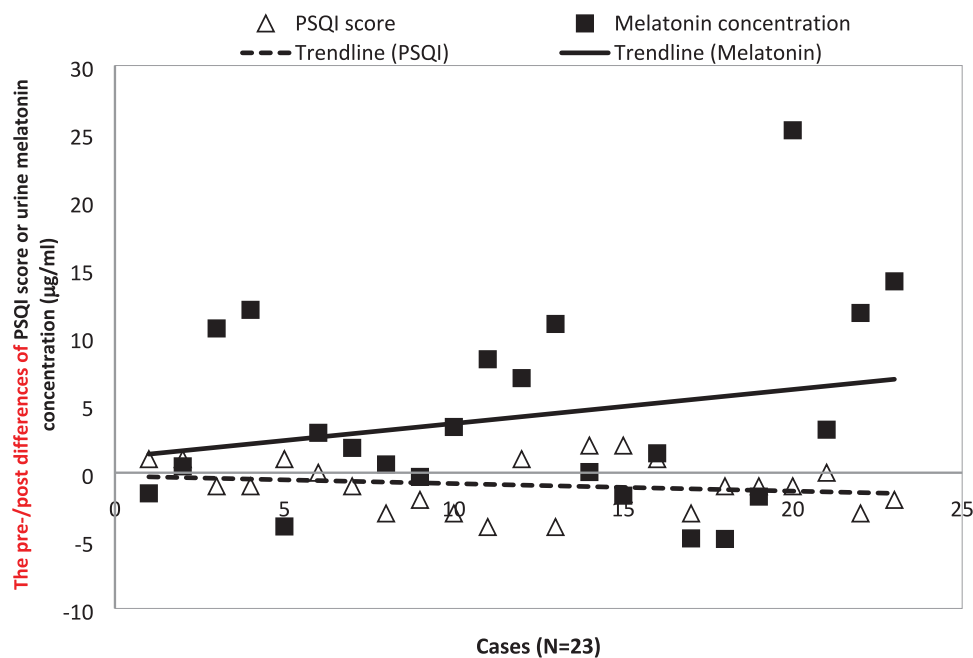
Wilcoxon signed-rank test was statistically significant, indicating a significant difference in median values between the pretest and post-test. Subtracting the post-test urinary melatonin concentration from the pretest urinary melatonin concentration yielded 7 negative ranks and 16 positive ranks, indicating that 16 of the post-test scores were greater than those of the pretest, and seven were less than those of the pretest. The post-test urinary melatonin concentration was significantly higher than that of the pretest; that is, the urinary melatonin concentration of patients with bladder cancer increased significantly after treatment, and the result was statistically significant (Table 2).

Figure 1 shows the difference in the mean values of melatonin concentration and PSQI score before and after treatment in 23 bladder cancer patients, and the trend of improvement. The overall melatonin concentration significantly increased after treatment ( $p < 0.05$ ), showing a clear improving trend. The global PSQI score significantly decreased after treatment ( $p < 0.05$ ). The overall sleep quality showed a trend of gradual improvement.

The life resilience data analysis was conducted according to the seven subscales of the original scale. First, in accordance with the description of questionnaire item conversion and scoring,

exploratory factor analysis (EFA) was used to test the sub-construct validity of the scale. In this study, the Kaiser–Meyer–Olkin value of the life resilience scale was 0.652 (degrees of freedom = 105,  $p < 0.001$ ). After the analysis, only 15 items remained, and four dimensions were obtained: ‘family resources,’ ‘future organizational style,’ ‘personal strength,’ and ‘social skills.’ The explanatory variances were 24.940%, 21.917%, 19.033%, and 11.706%, respectively, and the cumulative explanatory variance was 77.596%. The overall reliability of the 15 items was a Cronbach’s  $\alpha$  of 0.879, and the Cronbach’s  $\alpha$  of the 4 dimensions was 0.858, 0.873, 0.800, and 0.699, respectively. The Z score was  $-0.418$  ( $p = 0.676$ ), indicating no significant difference in the median pretest and post-test values (Table 2).

Next, the composition results of the four dimensions were examined. The mean value of the overall life resilience of the subjects was 5.301 (SD=0.915) and 5.333 (SD=0.722) before and after treatment, respectively, the mean value of ‘family resources’ was 5.269 (SD=1.366) and 5.365 (SD=1.004), respectively, the mean value of ‘future organizational style’ was 4.913 (SD=1.291) and 4.956 (SD=0.897), respectively, the mean value of ‘personal strength’ was 5.478 (SD=1.158) and 5.434 (SD=1.147), respectively,



**Figure 1.** Scatter plots with trendlines showing the pre-/post-difference of PSQI score and melatonin concentration after treatment.

and the mean value of 'social skills' was 5.695 (SD=0.958) and 5.681 (SD=0.825), respectively. The results showed that among the four dimensions evaluated before and after treatment, 'social skills' scored the highest, whereas 'future organizational style' scored the lowest. Among these four dimensions, the score for 'family resources' improved the most. A comparison of the overall life resilience and individual factors before and after the test did not show a statistically significant difference ( $p > 0.05$ ), indicating no significant change in the life resilience of individual subjects before and after treatment.

### Discussion

According to the 2018 global cancer statistics report, the incidence of bladder cancer in males is approximately four times higher than that in females.<sup>4</sup> Among the 67 initially examined patients in this study, the ratio of male-to-female patients was 10:3, which was slightly different from that of the global statistics. According to the 2016 Taiwan official cancer registry annual report, the incidence of bladder cancer increases annually. The ranking of the male cancer rate rose from 10th in the previous year to 9th in the current year. The ratio of male-to-female patients was approximately 3:1, which is comparable with that found in this study.<sup>20</sup>

Melatonin plays an important role in the 24h circadian rhythm of the human sleep-wake cycle, and it also has a protective effect on the human body and is key in facilitating falling and remaining asleep. Studies have shown that melatonin secretion is higher at night and has reduced release as daylight exposure increases. Its secretion at night has an inhibitory effect on sleep disorders.<sup>13</sup> Reduced melatonin secretion is associated with the formation of tumor cells.<sup>13</sup> It has been demonstrated in the literature that melatonin is a strong antioxidant that eliminates free radicals from the body, significantly inhibits the proliferation of bladder and prostate cancer cells, and induces the apoptosis of cancer cells, thereby playing an important role in the prevention and treatment of cancer progression.<sup>1,21</sup> From measuring the levels of 6-sulfatoxymelatonin in the nocturnal urine of women with breast cancer, it was determined that women with low levels of 6-sulfatoxymelatonin had an increased risk of breast cancer, as these levels and breast cancer showed a statistically significant negative correlation.<sup>12</sup> In this study, the melatonin concentration

of three patients after treatment was still lower than the mean value of the same age group, possibly because the urine samples were collected in the daytime, and it was difficult to achieve consistency. Nevertheless, there were still 20 patients who had a melatonin level higher than the mean value of their age group, showing that after treatment, the melatonin level not only increased but was also higher than the mean value of the same age group, reflecting better sleep quality. Similar to those reported in the literature, these results showed that an elevated melatonin concentration improves mood, effectively regulates the sleep disruption rhythm, and gradually restores good sleep quality.

Patients with bladder cancer, due to disease characteristics or organ functions affected by cancer cell invasion, may develop nocturia due to reduced urine output, which can easily lead to sleep disorders.<sup>16</sup> Research has shown that disrupted sleep rhythms can lead to the development of cancer and increase the risk of cancer, and that people who do not have sufficient or quality sleep are more likely to develop depression in the future, affecting their health and quality of life.<sup>22</sup> A study on bladder problems affecting sleep quality at night showed that the reasons more than half of the patients complained of sleeping for 6h or fewer were mostly bladder symptoms such as bladder pain, urinary urgency, or the need to go to the toilet, resulting in poor quality of life ( $p < 0.001$ ).<sup>23</sup> The research revealed a strong link to the symptoms of depression or anxiety, exerting a considerable influence on mental health. Therefore, there is an urgent need for healthcare personnel to provide related diagnosis and treatment, as well as prognostic management and services to reduce sleep disorders in cancer survivors.<sup>24</sup>

The average sleep time of the patients in this study was approximately 6.87h after treatment. Although most of the patients also claimed to have good sleep quality, a detailed analysis of the data showed that 34.8% of the patients did not fall asleep within 30 min, more than three times in the month before treatment, while only 17.4% remained affected after treatment, representing a 50% improvement. Usually, the sleep disruption frequency increases as one grows older or is under the influence of severe disease, leading to a decline in the total sleep hours and the deep-sleep period. Because the average age of the patients in this study was 66 years, the results showed that after

treatment, the sleep disruption frequency was reduced, which was possibly attributed to the gradual recovery of body functions after treatment and the reduction in factors that interfere with disease symptoms. Generally, night sleep disruption is considered an important factor affecting sleep quality and melatonin secretion. However, the daily life of bladder cancer patients, due to the symptoms of bladder problems caused by the disease, may perhaps be more affected than that of normal people. Melatonin secretion increases significantly after treatment. The overall trend lines of the PSQI and urinary melatonin showed a linear upward trend, making the long-term improvement effect of sleep quality worth further investigation. Therefore, in terms of care, it is necessary to address the disease as soon as possible based on the symptoms of each individual case to help the patient have better quality sleep.

Resilience refers to the ability of an individual to have certain traits or behaviors that protect them from stress or frustration due to personal or environmental interactions, allowing the individual to regain self-control and develop coping strategies for health.<sup>25</sup> In addition to alleviating the adverse reactions caused by the disease, patients with good life resilience can also develop positive adaptive energy and adjust their life patterns to cope with the impacts of physiological, psychological, and social factors, thus improving their quality of life.<sup>18,26</sup> Changes or increases in resilience, depending on the result of the interaction between individuals and the environment, are only a reflection of successful adaptation under stressful situations.<sup>27</sup> According to the sub-outcome of this study, the resilience of social ability is the strongest among the four dimensions, showing that the social function of an individual allows good interpersonal interactions and the active use of resources and indeed, reflects the relationship between personality traits and stress-coping attitudes.

According to the socio-emotional selectivity theory, with increasing age, human emotional regulation changes, in that it is gradually realized that human life is finite; therefore, attention to things is converted to positive thinking and behavioral patterns, the pursuit of a meaningful life is increasingly emphasized emotionally, and the more cognitive and behavioral resources are invested in, yield greater happiness.<sup>28</sup> The age range of the subjects who participated in this

study was quite wide; the physical stress, mental stress and adjustment ability of the subjects when facing the impact of disease and daily life vary with age, and the degree of damage to their physical and mental health differs as well. Compared with younger subjects, older subjects have high emotional stability and good emotion regulation skills. Under stressful situations, their moods and emotional responses are slow and do not fluctuate considerably; therefore, they are comfortable in accepting several changes and adversities. In this study, patients above the age of 60 years accounted for 82.6% of the total population, which perhaps explains why the results on life resilience failed to show a statistically significant difference.

Additionally, according to the 2016 cancer treatment and survivorship statistics reported by the American Cancer Society, the 5-year survival rate of bladder cancer patients of all stages was 77%, and the 10-year and 15-year survival rates were reduced to 70% and 65%, respectively.<sup>29</sup> Thus, the negative psychological responses, adverse effects and stress that bladder cancer patients face are not very strong, which may also explain why there was no significant difference in life resilience in this study.

The results of this study showed that overall life resilience nearly averages on the scale, possibly because follow up was carried out for only 3 months after treatment. However, the improvement in resilience within a short period is still quite limited. If the medical and nursing staff can make good use of the emotional advantages of the elderly and provide physical and mental interventions and support as early as possible, they will effectively assist the patients in improving their positive energy to survive cancer and treatment.

Although literature suggests that urinary melatonin secretion is higher at night than during the day, it is difficult to carry out urine sampling at night because patients have to co-operate with physicians' diagnosis and treatment time. For this reason, urine samples were collected during daytime both before and after treatment, thus the measured 6-sulfatoxymelatonin levels were lower than those at night. Nevertheless, the results of this study showed a statistically significant increase in urinary melatonin concentration after treatment. Future studies can be geared in the direction of night urine collection to further confirm the observation.

### Conclusion

In this study, using urinary melatonin as a physiological indicator as well as a questionnaire, we monitored and compared the improvement in sleep quality and life resilience of bladder cancer patients before and after treatment. Although the number of patients in this study was small, the data collected thus far showed that the number of male patients with bladder cancer was higher than that of female patients, the overall melatonin concentration significantly increased after treatment, and sleep quality also significantly improved. In terms of life resilience, 'family resources' is the strongest factor for resilience, indicating that patients rely on family resources during recovery. If patients can obtain more satisfaction from family support, they will have better resilience, which could be an important reference for medical and nursing care.

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### Author contributions

Dr Tse-Chou Cheng was responsible for examining patients, treatment, follow up, participation in the study process, formal analysis and investigation, and funding acquisition.

Ms Yi-Hua Lee was responsible for performing the literature review, applying for IRB approval and drafting the manuscript.

Associate Professor De-Chih Lee was responsible for the interpretation of statistical and research results.

Assistant Professor Yuan-Ping Chang was responsible for the research plan and implementation, data collection, preparation of the original draft, review and editing of the manuscript, submission of the manuscript, and supervision of the study.

### Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author.

### Conflict of interest statement

The authors declare that there is no conflict of interest.

### Ethics approval

This study was reviewed by the Institutional Review Board (IRB) of Chi Mei Medical Center, Taiwan (Approval No. 10405-L09).

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### Informed consent

Informed consent was obtained from all individual participants included in the study.

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### References

1. Chen YT, Yang CC, Shao PL, *et al.* Melatonin-mediated downregulation of ZNF746 suppresses bladder tumorigenesis mainly through inhibiting the AKT-MMP-9 signaling pathway. *J Pineal Res* 2019; 66: e12536.
2. Kwan ML, Kushi LH, Danforth KN, *et al.* The Be-Well study: a prospective cohort study of lifestyle and genetic factors to reduce the risk of recurrence and progression of non-muscle-invasive bladder cancer. *Cancer Causes Control* 2019; 30: 187–193.
3. Yu EYW, Wesselius A, Van Osch F, *et al.* The association between coffee consumption and bladder cancer in the bladder cancer epidemiology and nutritional determinants (BLEND) international pooled study. *Cancer Causes Control* 2019; 30: 859–870.
4. Bray F, Ferlay J, Soerjomataram I, *et al.* Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; 68: 394–424.
5. Turner MC, Gracia-Lavedan E, Cirac M, *et al.* Ambient air pollution and incident bladder cancer risk: updated analysis of the Spanish bladder cancer study. *Int J Cancer* 2019; 145: 894–900.
6. Schraufnagel DE, Balmes J, Cowl CT, *et al.* Air pollution and non-communicable diseases: a review by the forum of International Respiratory Societies' environmental committee. Part 2: air pollution and organ systems. *Chest* 2019; 155: 417–426.
7. Weiner AB, Keeter MK, Manjunath A, *et al.* Discrepancies in staging, treatment, and delays to treatment may explain disparities in bladder cancer outcomes: an update from the national



- cancer data base (2004–2013). *Urol Oncol* 2018; 36: 237.e9–237.e17.
8. El Turabi A, Abel GA, Roland M, *et al.* Variation in reported experience of involvement in cancer treatment decision making: evidence from the national cancer patient experience survey. *Br J Cancer* 2013; 109: 780–787.
  9. Bonomini F, Borsani E, Favero G, *et al.* Dietary melatonin supplementation could be a promising preventing/therapeutic approach for a variety of liver diseases. *Nutrients* 2018; 10: 1135.
  10. Carrascal L, Nunez-Abades P, Ayala A, *et al.* Role of melatonin in the inflammatory process and its therapeutic potential. *Curr Pharm Des* 2018; 24: 1563–1588.
  11. Cardinali DP. Melatonin as a chronobiotic/cytoprotector: its role in healthy aging. *Bio Rhythm Res* 2019; 50: 28–45.
  12. Schernhammer ES, Berrino F, Krogh V, *et al.* Urinary 6-sulfatoxymelatonin levels and risk of breast cancer in postmenopausal women. *J Natl Cancer Inst* 2008; 100: 898–905.
  13. Liu S, Madu CO and Lu Y. The role of melatonin in cancer development. *Oncomedicine* 2018; 3: 7–47.
  14. Viswanathan AN and Schernhammer ES. Circulating melatonin and the risk of breast and endometrial cancer in women. *Cancer Lett* 2009; 281: 1–7.
  15. Fang HF, Miao NF, Chen CD, *et al.* Risk of cancer in patients with insomnia, parasomnia, and obstructive sleep apnea: a nationwide nested case-control study. *J Cancer* 2015; 6: 1140–1147.
  16. Mossanen M, Brown JC and Schrag D. Well-being beyond the bladder. How do we improve the overall health of patients with bladder cancer? *BJU Int* 2018; 121: 489–491.
  17. Herrman H, Stewart DE, Diaz-Granados N, *et al.* What is resilience? *Can J Psychiatry* 2011; 56: 258–265.
  18. Yen J. Positive psychology. In: Teo T (ed) *Encyclopedia of critical psychology*. Springer, New York, 2014, pp.1431–1437.
  19. Buysse DJ, Reynolds CF III, Monk TH, *et al.* The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989; 28: 193–213.
  20. Ministry of Health and Welfare Taiwan. Taiwan cancer registry annual report, 2016. IOP Publishing PhysicsWeb, <https://www.hpa.gov.tw/Pages/Detail.aspx?nodeid=269&pid=10227> (2018, accessed 19 April 2019).
  21. Sainz RM, Mayo JC, Tan DX, *et al.* Melatonin reduces prostate cancer cell growth leading to neuroendocrine differentiation via a receptor and PKA independent mechanism. *Prostate* 2005; 63: 29–43.
  22. Chung WS and Lin CL. Sleep disorders associated with risk of prostate cancer: a population-based cohort study. *BMC Cancer* 2019; 19: 146.
  23. Troxel WM, Booth M, Buysse DJ, *et al.* Sleep disturbances and nocturnal symptoms: relationships with quality of life in a population-based sample of women with interstitial cystitis/bladder pain syndrome. *J Clin Sleep Med* 2014; 10: 1331–1337.
  24. Maguire R, Drummond FJ, Hanly P, *et al.* Problems sleeping with prostate cancer: exploring possible risk factors for sleep disturbance in a population-based sample of survivors. *Support Care Cancer* 2019; 27: 3365–3373.
  25. Johnson JL and Wiechelt SA. Introduction to the special issue on resilience. *Subst Use Misuse* 2004; 39: 657–670.
  26. Mahendran R, Lim HA, Chua J, *et al.* Psychosocial concerns of cancer patients in Singapore. *Asia-Pac J Clin Oncol* 2017; 13: e96–e103.
  27. Rutter M. Psychosocial resilience and protective mechanisms. *Am J Orthopsychiatry* 1987; 57: 316–331.
  28. Löckenhoff CE and Carstensen LL. Socioemotional selectivity theory, aging, and health: the increasingly delicate balance between regulating emotions and making tough choices. *J Pers* 2004; 72: 1395–1424.
  29. Miller KD, Siegel RL, Lin CC, *et al.* Cancer treatment and survivorship statistics, 2016. *CA Cancer J Clin* 2016; 66: 271–289.