Longitudinal Study on Changes of Cancer-Related Fatigue in Elderly Patients with Postoperative Chemotherapy for Non-Small Cell Lung Cancer

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Background: Cancer-related fatigue (CRF) stands out as one of the most prevalent subjective adverse reactions experienced by patients following chemotherapy, often resulting in unfavorable symptoms for elderly non-small cell lung cancer (NSCLC) patients during chemotherapy. Hence, the aim of this study was to explore the fluctuations in CRF levels among elderly NSCLC patients undergoing chemotherapy.

Methods: This retrospective study involved 400 elderly patients diagnosed with NSCLC. Standardized guidelines were employed to direct patient care following lung cancer surgery (T0), subsequent to the first (T1), second (T2), third (T3), and fourth (T4) cycles of chemotherapy. At various intervals, all patients underwent assessments utilizing the Piper Fatigue Scale, Karnofsky Performance Status (KPS) Scale, Pittsburgh Sleep Quality Index (PSQI) Scale, and Connor-Davidson Resilience Scale. Additionally, serum levels of IL-6 and TNF-α were quantified using enzyme-linked immunosorbent assay (ELISA).

Results: Throughout the treatment regimen, patients exhibited a declining trend in CRF, CD-RISC, and KPS scores ($p < 0.05$, T0 vs T4), whereas the PSQI score demonstrated a notable increase ($p < 0.05$, T0 vs T4). Furthermore, ELISA results revealed that as treatment advanced, the average levels of inflammatory markers interleukin 6 (IL-6) and tumor necrosis factor (TNF)-α during the T4 period significantly decreased compared to those at T0 ($p < 0.05$).

Conclusion: As the number of chemotherapy treatments for elderly NSCLC patients increased, the severity of CRF and the manifestations of sleep disorders were escalated. Additionally, physical function, psychological resilience, as well as IL-6 and TNF-α levels, exhibited a downward trend.

Keywords: cancer-related fatigue; elderly NSCLC patients; sleep disorders; physical function; psychological resilience

Introduction

With the aging of the population and the increasing global population, the incidence of tumors continues to rise annually. Among these, lung cancer stands out as one of the most prevalent malignancies worldwide, originating from the bronchial mucosa or glands. Its incidence and mortality rates rank highest among male malignant tumors. According to the global cancer statistics report, projected until 2020, there would be 2.2 million new cases of lung cancer and 1.8 million deaths globally, representing 22.4% of cancer incidence and 18.0% of mortality. Lung cancer ranks third in incidence and first in mortality worldwide [1]. Currently, in China, both the incidence and mortality rates of lung cancer are steadily increasing. Lung cancer is the second most common malignant tumor in terms of incidence and the leading cause of cancer-related deaths [2]. Recent cancer data from 2020 indicates approximately 820,000 new cases and 710,000 deaths from lung cancer in China, with lung cancer ranking first in both incidence and mortality among malignant tumors. Faced with challenges such as smoking, air pollution, and an aging population, the incidence and mortality rates of lung cancer in China continue to rise [1, 3].

The incidence of lung cancer notably rises with advancing age. According to data from the American Cancer Society (ACS), a significant portion of lung cancer cases is observed in individuals aged 65 and above. The average age at diagnosis for lung cancer is 70 years [4]. Furthermore, among all cancers in both males and females, lung cancer stands as the most prevalent and primary cause of death in individuals aged 85 and older [5]. Non-small cell lung cancer (NSCLC) represents the predominant subtype of lung cancer, accounting for approximately 85% of all newly diagnosed cases [6]. Surgical resection stands as the preferred treatment modality for early NSCLC patients, offering the best prospects for long-term survival [7]. This surgical treatment is primarily indicated for those with early-stage lung cancer, while chemotherapy serves as the most commonly employed adjuvant treatment.

Administered through various routes such as intravenous infusion, thoracic perfusion, and bronchial artery perfusion,

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the medication disseminates throughout the body via the bloodstream, exerting its therapeutic effects by targeting tumor cells and impeding disease progression [8]. Regrettably, the majority of NSCLC patients are diagnosed at advanced stages (III or IV), often characterized by metastasis, thus missing the opportunity for surgical intervention [9]. Only of 18% advanced NSCLC patients undergo surgical treatment, while nearly 62% receive radiation therapy and systemic treatments including targeted therapy, chemotherapy, and immunotherapy in efforts to enhance long-term survival [10].

Chemotherapy stands as the primary treatment approach for mid to late-stage lung cancer patients, delivering notable results in symptom reduction and enhancement of quality of life, with an overall efficacy rate exceeding 30% [11]. However, chemotherapy often induces varying degrees of fatigue in patients during and after treatment [12]. Cancer-related fatigue (CRF) emerges as a prevalent subjective adverse reaction following chemotherapy, affecting up to 90% of lung cancer patients. It presents a formidable challenge for practicing physicians to address [13]. CRF manifests as a multitude of symptoms that impede daily activities, social interactions, familial relationships, work performance, and role functioning, which often leads to unfavorable symptoms such as loss of appetite and fluctuations in emotional well-being [14]. Gaining insight into the symptoms experienced by lung cancer patients undergoing chemotherapy is beneficial for effective symptom management, thereby extending survival periods and enhancing the quality of life for these individuals.

Hence, this study delved into a comprehensive analysis of the patterns of CRF among elderly patients undergoing postoperative chemotherapy for lung cancer, shedding light on its incidence and severity. Such exploration holds promise in enhancing our comprehension of the underlying mechanisms driving this distressing symptom, thereby furnishing a foundation for its prevention and management strategies.

Materials and Methods

Participants

This study was conducted as a retrospective trial, involving a total of 400 patients who underwent postoperative chemotherapy for lung cancer at our hospital between June and October 2023. Inclusion criteria comprised: (1) patients met the clinical diagnostic criteria of NSCLC as per the American Joint Committee on Cancer seventh edition criteria [15] and confirmed through postoperative pathological examination; (2) age $\geq$ 60 years; (3) receipt of chemotherapy without interruption; (4) possessing adequate understanding and language expression abilities, as well as good compliance. Exclusion criteria included: (1) participation in other clinical trials; (2) Karnofsky Performance Status (KPS) scores $<$60 indicating poor physical function [16]; (3) presence of life-threatening diseases or concurrent malignant tumors; (4) current or past history of consciousness disorders or mental illness; (5) lack of awareness regarding lung cancer diagnosis; (6) anticipated survival time of $<$6 months.

Study Design

Data Collection

Based on the review of relevant literature, demographic and clinical data that could potentially influence outcome indicators were incorporated. Demographic data encompassed age, gender, payment method, education level, marital status, medical burden, and other relevant factors. Clinical data included disease diagnosis, cancer staging, treatment regimen, presence of chronic diseases (e.g., diabetes, hypertension, chronic obstructive pulmonary disease), pain scores, nutritional status, sleep patterns, laboratory indicators, and additional pertinent parameters.

Sample Size

The trajectory model necessitates a minimum sample size of 200 [17]. For this study, 200 patients were pre-enrolled, with an additional buffer of 10% to account for potential dropout, resulting in a minimum acceptance of 220 patients. Additionally, to ensure an adequate sample size considering hospital accessibility, 400 patients were recruited. All patients provided informed consent prior to participation. Approval for this study was obtained from Shanghai Chest Hospital ethics committee.

Survey Methods

A total of four chemotherapy cycles constituted one treatment course spanning 4 months. Standardized guidelines were employed to direct patient care after lung cancer surgery (T0), following each chemotherapy session: after the first (T1), second (T2), third (T3), and fourth (T4) cycles. All questionnaires were formulated by uniformly trained investigators and researchers and administered to eligible participants. In instances where subjects were unable to independently complete the questionnaire due to various reasons, investigators neutrally and non-leadingly read the questions to the patients, aiding them in comprehending the content before assisting in questionnaire completion. Subsequently, all questionnaires were collected on-site.

Piper Fatigue Score

The Revised Piper Fatigue Scale (PFS-R), initially introduced by Piper *et al*. [18] in 1998, underwent subsequent revisions, ultimately comprising of 22 items. The scale describes four dimensions of subjective fatigue, delineated by the following subscales: behavioral severity, cognitive severity, affective meaning, and sensory/emotional severity. Each of the 22 items is rated on a scale from 0 to 10, with 0 indicating the most favorable condition and 10 indicating the most unfavorable. Subscale scores are derived, by summing the scores of all items within the respective

subscale and dividing by the number of items. In cases where data is missing but patients have answered to at least 75–80% of the questions, the average is computed based on the number of completed items (e.g., summing the values of four completed items and dividing by 4). Add up the scores of the 22 items and divided by 22 to calculate the total PFS-R score. The scoring explanation is as follows: 0 point indicates absent, 1–3 points indicate mild, 4–6 points indicate moderate, and 7–10 points indicate severe [19].

The Karnofsky Performance Status (KPS)

Score was utilized to assess the physical functional status of patients. This scale ranges from 0 to 100 points, with increments of 10 [20]. Higher scores indicate better health condition and quality of life.

Pittsburgh Sleep Quality Index (PSQI)

The measurement of sleep quality utilized the Mandarin Chinese version of the Pittsburgh Sleep Quality Index (PSQI) questionnaires [21]. This instrument comprises 19 self-rated sleep behavior questions, categorized into 7 subdomains: sleep latency, subjective sleep quality, sleep duration, sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction. Each question is rated on a 3-point Likert scale. The Cronbach's α coefficient ranges from 0.81 to 0.85, indicating good internal consistency. Scores on the PSQI range from 0 to 21, with a score of ≥ 7 indicating the presence of sleep problems, and higher scores indicating poorer sleep quality.

Connor-Davidson Resilience Scale (CD-RISC) 10

Psychological resilience was assessed using the Connor-Davidson Resilience Scale (CD-RISC) [22]. This scale comprises 25 questions, with scores ranging from 0 to 4 for each question. Consequently, the total score ranges from 0 to 100 points, with higher scores indicating greater resilience. The CD-RISC encompasses five factors: personal competence, trust in one's intuition, positive acceptance of change, control, and spiritual influence. Widely regarded as a reliable and effective measure of psychological resilience, the CD-RISC is a valuable tool for assessing an individual's resilience. In this study, the Chinese version of the CD-RISC was employed, demonstrating robust psychometric properties and serving as a reliable and effective means of evaluating psychological resilience.

Outcomes

The primary outcome measure is the absolute change in the total score on the Piper Fatigue Scale from the postoperative lung cancer surgery (T0) period to the conclusion of the fourth chemotherapy treatment (T4) period. The secondary outcome measures encompass the relative change (percentage change) in the total PFS score, along with the absolute changes in KPS scores, PSQI scores, CD-RISC scores, and levels of inflammatory markers interleukin 6 (IL-6) and tumor necrosis factor (TNF)-α.

Enzyme-Linked Immunosorbent Assay (ELISA)

Serum levels of interleukin 6 (IL-6) and tumor necrosis factor (TNF)-α were quantified using enzyme-linked immunosorbent assay (ELISA) methods (H007-1-1, H052-1-2; Nanjing Jiancheng Bioengineering Institute, Nanjing, China). Fasting blood samples of 5 mL were collected from patients in the morning, and the serum samples were stored at –20 °C for subsequent testing.

Statistical Analysis

The data were analyzed using SPSS 24.0 software (IBM Corp., Armonk, NY, USA). Measurement data conforming to a normal distribution are presented as mean $\pm$ standard deviation ($\bar{x} \pm$ s), while count data are expressed as the number of cases and percentage. The *t*-test was employed for data analysis, with statistical significance defined as $p < 0.05$.

Results

Participants and Baseline Characteristics

In this study, 400 eligible elderly patients who underwent chemotherapy following lung cancer surgery were included, and all completed the study as scheduled. Table 1 presents the baseline and clinical characteristics of the participants. The average age of the 400 participants was (66.2 $\pm$ 1.9) years old, with 210 being male patients, the majority of whom presented with stage III-IV tumors. Social demographic data, including education level, marital status, medical burden, presence of chronic diseases, etc., were also subjected to statistical analysis.

All enrolled patients underwent a total of four cycles of chemotherapy over a span of four months. PFS-R survey was administered to all patients at five time points, and the results are presented in Table 2. PFS-R scores for the participants were categorized into four dimensions. The total PFS-R score was lowest at the T0 time point, gradually increasing with each of the four chemotherapy treatments, reaching its highest point after the fourth chemotherapy cycle. Notably, among all dimensions, the sensory dimension exhibited the highest score. Statistical analysis using the *t*-test revealed significant differences in PFS-R scores across these five time points ($p < 0.05$).

Furthermore, we examined the KPS, PSQI, and CD-RISC scores of patients at various time points, as depicted in Table 3. The findings revealed a decline in KPS scores among lung cancer patients undergoing chemotherapy after four cycles, indicating a notable decrease in physical functional status compared to the T0 period, particularly evident from the T2 period onwards ($p < 0.05$). Similarly, the CD-RISC scores exhibited a gradual decrease, signifying a decline in patients' mental resilience, with significant differences observed among the results at each time point ($p < 0.05$). Conversely, the PSQI scores showed an upward trend throughout the chemotherapy process, indicative of deteriorating

Table 1. Baseline characteristics of the patients.

Characteristic	Cases n = 400 (%)
Age	
Years, mean ± SD	66.2 ± 1.9
Gender	
Male	210 (52.5)
Female	190 (47.5)
Educational level	
Elementary school and junior high school	278 (69.5)
High school and technical secondary school	68 (17)
University or college education	54 (13.5)
Marital status	
Life with spouse	305 (76.2)
Unmarried, widowed, or divorced	95 (23.8)
Medical burden	
Yes	246 (61.5)
No	154 (38.5)
Cancer staging	
I∼II period	90 (22.5)
III∼IV period	310 (77.5)
Comorbidities	
Yes	298 (74.5)
No	102 (25.5)

Table 2. PFS-R scores at different time points.

	T0	T1	T2	T3	T4
Behavioral dimension	5.7 ± 0.8	5.9 ± 1.1[a]	6.3 ± 0.6[ab]	6.6 ± 0.9[abc]	6.9 ± 0.5[abcd]
Cognitive dimension	4.5 ± 0.3	4.8 ± 0.7[a]	5.2 ± 0.5[ab]	5.4 ± 0.5[abc]	5.5 ± 0.8[abc]
Affective meaning dimension	5.6 ± 0.9	5.8 ± 0.8[a]	6.3 ± 1.1[ab]	6.7 ± 0.7[abc]	6.9 ± 0.7[abcd]
Sensory dimension	6.2 ± 1.1	6.3 ± 0.7	6.7 ± 0.4[a]	7.2 ± 0.6[ab]	7.4 ± 0.4[abc]
Total PFS-R Score	22.0 ± 1.7	22.8 ± 1.9[a]	24.5 ± 1.5[ab]	25.9 ± 1.5[abc]	26.7 ± 1.5[abcd]

[a]$p < 0.05$ vs T0 period, [b]$p < 0.05$vs T1 period, [c]$p < 0.05$ vs T2 period, [d]$p < 0.05$ vs T3 period.

sleep quality. Notably, a PSQI score exceeding 7 at the T4 time point indicated persistent sleep disorders among patients.

The findings indicated that as treatment progressed, the average levels of inflammatory markers IL-6 and TNF-α markedly decreased compared to those at the T0 period (Table 4) ($p < 0.05$). Consequently, with the administration of chemotherapy, patients experienced a significant improvement in inflammatory symptoms compared to their pre-treatment status.

Discussion

In this longitudinal study, we investigated the changes in CRF at five time points: T0 (post-surgery), T1 (after the first chemotherapy), T2 (after the second chemotherapy), T3 (after the third chemotherapy), and T4 (after the fourth chemotherapy) in elderly lung cancer patients following surgery. Our aim was to assess the occurrence and severity of CRF at these different time intervals. Given the unique condition and physical state of each patient, the regimen and dosage of multiple chemotherapy treatments were adjusted accordingly.

Throughout the study, KPS, PSQI and CD-RISC scores of the participating patients were evaluated at different time nodes. Our findings revealed a consistent trend: the total PFS-R score was lowest at the T0 time point, gradually increasing after each chemotherapy treatment, and peaking at the T4 time point. Additionally, KPS scores and CD-RISC scores exhibited a similar upward trajectory with increasing chemotherapy cycles, indicative of improved physical function and mental resilience over time. Conversely, PSQI scores demonstrated a upward trend, indicating a decline in sleep quality throughout the chemotherapy process.

Furthermore, our investigation into inflammatory markers revealed a significant reduction in the levels of IL-6 and TNF-α after the fourth chemotherapy cycle, suggesting an improvement in inflammatory symptoms among patients following treatment.

Systemic chemotherapy, while commonly employed in the treatment of NSCLC, often yields limited efficacy and is accompanied by severe adverse reactions, such as gastroin-

Table 3. The change of each scale at different time points.

	T0	T1	T2	T3	T4
KPS score	78.6 ± 5.5	77.3 ± 6.8	76.5 ± 6.5^{ab}	74.9 ± 7.2^{ab}	73.6 ± 8.1^{abc}
PSQI score	7.6 ± 1.1	8.8 ± 0.7^{a}	10.6 ± 1.6^{ab}	11.8 ± 1.3^{abc}	12.4 ± 2.1^{abcd}
CD-RISC	64.6 ± 11.3	61.3 ± 9.7^{a}	59.6 ± 10.6^{ab}	56.7 ± 11.4^{ab}	53.8 ± 9.2^{abcd}

[a]$p < 0.05$ vs T0 period, [b]$p < 0.05$vs T1 period, [c]$p < 0.05$ vs T2 period, [d]$p < 0.05$ vs T3 period.

Table 4. Serum levels of interleukin 6 (IL-6) and tumor necrosis factor (TNF)-α during T0 and T4 points.

	T0	T4
IL-6 (pg/mL)	14.6 ± 0.3	12.3 ± 0.6^{a}
TNF-α (pg/mL)	45.3 ± 0.9	36.8 ± 1.5^{a}

[a]$p < 0.05$ vs T0 period.

testinal disturbances, hematological toxicity, and liver and kidney damage, significantly compromising the quality of life for NSCLC patients [23]. CRF represents a prevalent and distinctive symptom among lung cancer patients, exerting a profound impact on their quality of life and emotional well-being [24, 25]. Reports indicate that CRF affects up to 96% of lung cancer patients, with chemotherapy recipients experiencing a staggering 80% incidence rate. Moreover, CRF frequently leads to treatment interruptions and adverse prognoses [25]. Characterized by multifaceted symptoms that impede various aspects of daily life, CRF can induce unpleasant manifestations such as loss of appetite and alterations in emotional state [14].

The etiology of CRF is complex and remains largely elusive, though several theories have been posited. Skeletal muscle dysfunction and dysregulation of inflammatory cytokines are among the proposed mechanisms [26]. Notably, anti-cancer therapies play a pivotal role in activating pro-inflammatory cytokine networks, potentially triggering the onset of CRF through cytokine signaling within the central nervous system [27].

Inflammation serves as a prominent avenue of research linking cancer and fatigue. Numerous cross-sectional studies have underscored the association between fatigue and circulating inflammatory cytokines, including interleukin-6 (IL-6), C-reactive protein (CRP), soluble tumor necrosis factor receptors (sTNFRs), and tumor necrosis factor (TNF)-α in cancer patients [28, 29]. IL-6 holds particular significance in NSCLC and tumor metastasis. Elevated IL-6 levels have been implicated in conferring resistance to molecular targeted therapy for lung cancer, while circulating IL-6 levels may serve as prognostic markers in NSCLC patients [30, 31]. Moreover, studies have established a close association between IL-6 and TNF-α levels and the progression of NSCLC. As cancer pain intensifies in NSCLC patients, circulating IL-6 and TNF-α levels tend to rise gradually, correlating positively with VAS pain scores. This underscores the relationship between inflammatory markers and cancer-related symptoms [32].

In the present study, levels of IL-6 and TNF-α were higher in lung cancer patients during the T0 period compared to the T4 period, indicating a reduction in inflammatory symptoms following four chemotherapy treatments. Lower levels of IL-6 and TNF-α also portend a more favorable prognosis, suggesting the potential utility of these markers in prognostic assessment.

In cancer patients, CRF often coexists with other symptoms, such as sleep disorders. Therefore, this study not only examined the changes in CRF among elderly lung cancer patients undergoing chemotherapy but also assessed their sleep quality, physical condition, and mental resilience. This comprehensive approach aimed to elucidate the alterations in these indicators during the course of chemotherapy.

CRF and sleep disorders are distinct yet interconnected conditions sharing common biological mechanisms [33]. Nearly all cancer patients, irrespective of age, treatment modality, cancer type, or disease stage, experience some degree of fatigue, with up to 75% experiencing sleep disturbances. Importantly, these symptoms can persist for several years post-treatment. Furthermore, sleep disorders can exacerbate daytime fatigue, precipitate neurocognitive deficits, and contribute to emotional disturbances.

The overall PFS-R score among lung cancer patients exhibited a consistent upward trajectory throughout the treatment cycle. Comparatively, at the T4 time point, the fatigue score was the lowest, while the PSQI score was the highst, indicating heightened CRF and sleep disturbances at this juncture. Consistent with our findings, previous research has observed that during the fourth chemotherapy cycle, patients exhibited markedly more severe sleep disturbances and CRF across all dimensions compared to earlier stages [34].

Beyond sleep disturbances, physical pain is intricately linked with psychological factors, leading to functional alterations in patients' mood, cognition, and behavior. This interplay often precipitates a cascade of negative emotions such as anxiety and depression, further triggering or exacerbating CRF and detrimentally impacting patients' quality of life [35]. Specifically, clinical levels of sleep disturbances have been significantly associated with elevated levels of emotional distress among patients undergoing chemotherapy [36].

Psychological resilience, a quality that shields individuals from adverse or traumatic experiences, aligns with the principles of positive psychology and exerts a soothing influ-

ence on challenging behaviors [37]. CD-RISC serves as a tool to gauge a patient's mental resilience, offering insights into the severity of their negative emotions. Despite conventional treatment modalities primarily focusing on enhancing therapeutic efficacy and survival rates, patients' psychological well-being is often overlooked, thereby impacting patient compliance to some extent and impeding postoperative recovery [38].

In our study, CD-RISC scores were highest at the T0 time point, gradually declining over the course of chemotherapy and reaching their lowest at the T4 time point. This suggests a decrement in patients' mental fortitude and a gradual increase in negative emotions during treatment. Notably, the trend in CD-RISC scores mirrored that of CRF, with both exhibiting more pronounced changes throughout the chemotherapy regimen. Research has demonstrated that implementing relevant interventions can bolster the psychological resilience of cancer patients, diminish their levels of depression and anxiety, reduce the severity of CRF, and enhance their quality-of-life following surgery [39].

Physical function holds significant weight in the decision-making process for oncologists when selecting anti-cancer treatments. An illustrative example of such a decision is the choice between concurrent chemoradiation and sequential chemoradiation for locally advanced unresectable lung cancer [40]. KPS scale is commonly employed to evaluate the physical performance of patients across various treatment regimens for NSCLC [23, 40, 41].

Among the five time points assessed, patients at the T0 time point exhibited the lowest Total PFS-R score, indicating the least overall fatigue. Concurrently, the average KPS score of patients at this time point surpassed that of the other four time points, signifying good health status before commencing chemotherapy. Conversely, at the T4 time point following completion of the chemotherapy regimen, patients demonstrated higher fatigue scores and lower KPS scores, both of which were inversely correlated, consistent with findings from previous studies. Indeed, higher fatigue scores have been associated with lower KPS scores [42]. Our research aligns with these previously reported findings.

Conclusion

Overall, this study elucidated that as the number of chemotherapy treatments increased for elderly patients with NSCLC, the severity of CRF escalated, while the incidence of sleep disorders, decline in physical function, and diminishing mental resilience exhibited a declining trajectory. These observed patterns of change can equip doctors and family members with valuable insights to better support patients and enhance their physical and mental well-being. The diminished levels of IL-6 and TNF-α, indicative of reduced inflammation in patients, may serve as prognostic indicators for a more favorable outcome. However, it is worth noting that the baseline information of the patients included in our investigation was not comprehensive enough, warranting further exploration in future studies.

Availability of Data and Materials

The data used to support the findings of this study are included within the article, and during the present study are available from the corresponding author on reasonable request.

Author Contributions

TTW, HC and YW made substantial contributions to the conception and design of the study, wrote and revised the manuscript. YQL collected the data and analyzed as well as interpreted the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by Shanghai Chest Hospital Medical Ethics Committee (KS23020) and complied with the Declaration of Helsinki. The whole process of the experiment was informed consent of the patients or their families.

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Conflict of Interest

The authors declare no conflict of interest.

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