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台灣地區呼吸器依賴病人之發生率、生活品質、及成本效果研究

Incidence rates, quality of life and cost-effectiveness of patients under prolonged mechanical ventilation in Taiwan

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台灣地區呼吸器依賴病人之流行病學、生活品質、存活壽命及成本效果研究
Epidemiology, quality of life, survival and cost-effectiveness of patients under prolonged mechanical ventilation in Taiwan

本論文係洪美娟君（D96841003）在國立臺灣大學職業醫學與工業衛生研究所、所完成之博士學位論文，於民國 101 年 3 月 24 日承下列考試委員審查通過及口試及格，特此證明

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完成博士學位一直是我碩班畢業後10年的心願，首先要把這榮耀獻給上帝，辛勤指導我的老師王榮德教授，及我親愛的家人。亦感謝在校期間師長在各領域上的啟發與教導，學長姐的不吝指教，同學的相互打氣，研究團隊們各項支援，包括國衛院麗光老師與信銘、嘉義基督教醫院陳院長、林主任、范醫師、嚴元鴻醫師與欣諺、台大醫院蔡甫昌醫師、余忠仁醫師與郭律成醫師、陽明醫學大學施富金老師，台大神經部鄭建興醫師、中央研究院黃景祥老師、台大心理系姚開屏老師、台大職能治療系謝清麟老師，及郁瑩、正芬、淑如、建瑋與玉嬋。另外，感謝受訪醫院、受試者及其家屬接受訪談，還有國衛院及國科會經費的贊助。

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摘要

研究目的：

本論文研究之主要目的為：(1)探討呼吸器依賴病人每年發生率 (incidence rates) 、共病 (co-morbidity) 聚集情形與預期壽命；(2)測量呼吸器依賴病人之生活品質：病人、家屬及護理人員的比較；(3)估算呼吸器依賴病人之調整生活品質後的預期壽命 (quality-adjusted life expectancy, QALE)及調整生活品質後損失的預期壽命；(4)估算呼吸器依賴病人之共病的遞增成本效用比值 (incremental cost-effectiveness ratio, ICER）。

研究背景：

公衛的核心價值是全體人類的健康，為達成此目標，國家必須有相對的配套措施。台灣很幸運的 1995 年 3 月全民健保實施，人民就醫機會逐漸均等不怕看病，並針對重大傷病族群予以免部份負擔，包括洗腎、呼吸器使用超過 21 天病人...等，使得人民不必因病而貧，目前已照顧到超過 99%全體國人的健康。但也因此造成國家財政的重大負擔。依據中央健保局在 2010 年所公佈的重大傷病醫療費用前六大疾病，長期呼吸器依賴(呼吸器使用超過 21 天)的病人排名第二位，總支出每年約為新台幣 170 億。為同時顧及照護品質、效率及醫療資源的分配正義，以讓健保永續經營；我們必須開始思考不同的照護策略，包括先了解此類病人之發生率、生活品質、存活及成本效果。

長期呼吸器依賴(Prolonged mechanical ventilation or ventilator dependent) 發生背景：

由於全國加護病床有限，許多長期依賴呼吸器患者佔用急性病房或甚至加護病房，導致急症患者面臨一床難求。健保局多方考量下，於 1998 年提出「改善醫院急診重症醫療計畫」，訂定「急性呼吸治療病床」及「呼吸照護病床」之設置標準，2000 年提出「全民健康保險呼吸器依賴患者整合性照護前瞻性支付方式」試辦計畫迄今這幾年來，此類病人雖然其增加的幅度藉由”整合性傳送服務”(Integrated delivery services)的介入自 2005 年後有延緩的趨勢，有關生命倫理公正性及成本效果的問題持續存在。這需要由中央健康保險局根據各種病人之存活與生活品質，與所有涉及此事的參與者(病人及其家屬、醫療照護人員與機構等)之共識，制定一套合乎醫學倫理之臨床指引來協助解決這個問題。目前國際間尚缺乏探討呼吸器

依賴病人在不同共病下，結合存活、生活品質及醫療花費的成本效果(cost-effectiveness)實證資料。

研究方法：

本論文研究以「以健保資料和對應之死亡檔登記資料所建立起的 1998-2007 年 50,481 筆呼吸器依賴案例全國代表性樣本長期追蹤資料庫」進行分析此類病人在不同疾病組合下之發生率及存活壽命；收集台灣北部醫學中心、中南部區域醫院，及其他呼吸治療醫院，使用 EQ-5D 歐盟生活品質問卷測量加護病房、呼吸照護中心、呼吸照護病房及居家照護之共 142 名呼吸器依賴病人的生活品質。並以嘉義基督教醫院 1998-2007 年間共有 633 名下轉至呼吸照護病房之呼吸器依賴病人，研究調整生活品質後的預期壽命及調整生活品質後損失的預期壽命。最後，結合 50,481 名病患之生病期間所有的醫療費用，計算其成本效果或生活品質調整後之人年(quality-adjusted life year, 簡稱 QALY 或健康人年)所負擔的費用。

結果與討論：

過去這 10 年來，呼吸器依賴病人成快速成長，每年約達兩萬人以上。其 17-85 歲累積發生率為 0.103 - 0.145，也就是說 17-85 歲的人口族群中，如果沒有死於其他疾病，約有 1/7 至 1/10 的機會將成為呼吸器依賴病人，應及早採取對策。在預期壽命方面，退化性神經性疾病、中風或一般外傷之呼吸器依賴病人似乎比癌症或慢性腎衰竭病人有較長的存活壽命；小於 85 歲的慢性阻塞性肺部疾病(Chronic Obstructive Pulmonary Disease)相較其他年齡層共病，也有較長的存活(第一章)。

在病人生活品質評估方面，具中等認知功能 (MMSE≧15, Mini-mental status examination)的病人，由主要照顧家屬評值個案之生活品質，似乎較接近個案自評的結果；喪失認知及溝通能力的病人，由主要照護家屬或護理人員評值病人生活品質，則無明顯的差異 (第二章)。

平均年齡 76 歲的呼吸器依賴病人之預期壽命為 1.95 年，所損失的預期壽命的為 8.48 年。在調整生活品質後的預期壽命，具中等認知功能，為 0.58 健康人年；約 60%喪失認知及溝通能力，為 0.28-0.29 健康人年。因呼吸器依賴而損失之調整生活品質後的預期壽命為 9.87-10.17 健康人年 ，顯示他們為極需醫療照護之健康弱勢族群(第三章)。

成本效果分析結果，認知功能差的病患，除肝硬化、一般外傷及小於 64 歲的菌血症或休克外，其每個健康人年均超過 58,000 元美金 (折合新台幣約 1,798,00 元)或

3 倍國內生產毛額(gross domestic product, GDP)；認知功能較佳，慢性腎衰竭、退化性神經性疾病或超過 85 歲的多重共病者亦是如此，似乎已超過世界衛生組織成本效果參考建議的每個健康人年約 1-3 倍 GDP。但在肝硬化、一般外傷及小於 65 歲的共病患者，則少於 1.4 倍 GDP。上述實證資料將可提供病人、家屬、醫療人員及醫療決策者在面臨病人是否接受長期呼吸插管決策，及資源分配之重要實證數據，並開啟彼此間的對話平台，最好及早預防走到此地步(第四章)。

結論：

整體而言，長期呼吸器依賴患者中某些特性病人之存活率、生活品質與成本效果不理想，值得作進一步更深入之分析探討，且在本國社會形成臨床決策之共識，以促進全民健保資源使用之公平性與效率。所有經呼吸治療救治超過 21 天仍需呼吸器維生者，除繼續進行呼吸器拔除訓練外 (weaning)，針對不可逆之無意識患者，請醫療團隊似可建議家屬，考慮轉為安寧療護以縮短病人痛苦。未來更應正視生命教育 (life education)，推廣在身體尚健康時，或疾病早期即簽署免予急救意願書 DNR (Do not resuscitate) ，以對加護及呼吸治療資源作最適當之運用。

關鍵詞: 呼吸照護、預期壽命、發生率、共病、生活品質、調整生活品後的預期壽命、成本效果

Abstract

Objective: The aims of our study are: (1) to determine the incidence rate (IR), median survival, life expectancies for different types or co-morbidities of patients undergoing prolonged mechanical ventilation (PMV) ; (2) to explore how much difference on the quality of life (QOL) assessments between patients under PMV and their proxies (family caregivers and nurses); (3) to estimate the quality-adjusted life expectancy (QALE) and the expected lifetime utility loss of different types of patients with PMV (4) and to estimate the incremental cost-effectiveness ratios (ICER) for different types of patients undergoing PMV.

Background: As we know, the core value of public health is health for all and the first step would be to achieve the goal of health care for all. In Taiwan, we are very fortunate to have developed the National Health Insurance (NHI) that implements a system of universal coverage (over 99% now) for all people of Taiwan. The NHI comprehensively covers various health care services, especially those of catastrophic illnesses, including maintenance hemodialysis for end stage renal disease and chronic ventilator use consecutively for more than 21 days, etc., which results in a tremendous financial burden and threatens the sustainability of the NHI. According to the reimbursement data of NHI in 2010, the prolonged mechanical ventilation (PMV) consumes the second highest in the average health expenditure with an annual total health expenditure of 17 billion NT (New Taiwan) dollars. In order to keep the sustainability of the NHI under good quality, efficiency and equitable distribution of resources at the same time, we began to think of different strategies. One of them is to explore the incidence rate, quality of life, survival, and cost effectiveness of the patients undergone prolonged mechanical ventilation. Although the increasing trend seems slowed down after the pilot implementation of IDS (integrated delivery service), the controversial issues of distributive justice on bioethics and cost-effectiveness of such cares still persist and may not be easily resolved without relevant information on the life expectancy and quality of life of different types of patients. To our knowledge, there has been few study that estimates the long term survival, quality of life, lifetime cost, and cost effectiveness together for PMV patients with multiple co-morbidities, which are the major goals of this dissertation.

Material and Methods: With the kind assistance from the National Health Research Institutes, we have just established a representative national longitudinal data of 50,481 cases who were ventilator dependent between 1998 and 2007. The data were linked with the reimbursement data of the NHI (National Health Insurance) and National Mortality Registration database of Taiwan. We used these databases of PMV to estimate IR, cumulative IR, and survival function, and quantitatively determine the QOL of patients using intensive care unit (ICU), RCC and RCW with the Taiwan version of EQ-5D questionnaire. Moreover, we applied latent class analysis (LCA) to re-classify these patients into several categories and determine their individual survival functions and extrapolated to 300 months in order to provide policy suggestions for proactive prevention. QOL measurements and lifetime survival functions were integrated together to calculate the quality-adjusted life expectancies for different types of PMV patients. Finally, we combined the data of lifetime health expenditures reimbursed by the NHI, and estimate the cost-effectiveness or incremental costs per quality-adjusted life year (QALY) according to different categories and/or clusters of diagnoses for these patients.

Results: The analysis of 50,481 PMV patients revealed that incidence rates increased as patients grew older and that cumulative incidence rates (17-85 years old) increased from 0.103 in 1998 to 0.183 in 2004 before stabilising thereafter. The life expectancies of PMV patients suffering from degenerative neurological diseases, stroke, or injuries tended to be longer than those with chronic renal failure or cancer. Patients with chronic obstructive pulmonary disease survived longer than did those co-morbid with other underlying diseases, especially septicaemia/shock (Chapter 1).

QOL assessments from family caregivers agreed more closely with patients than did those from nurses using EQ-5D evaluations for patients with clear cognition, but either proxy was acceptable for rating PMV patients with poor cognition (Chapter 2).

The average age of subjects was 76 years old. The life expectancy and loss of life expectancy were 1.95 years and 8.48 years, respectively. The QALE of 55 patients with partial cognitive ability and the ability to respond was 0.58 QALY, whereas the QALE of 87 patients with poor consciousness were 0.28 and 0.29 QALY for the EQ-5D measured by family caregivers and nurses, respectively. The loss of QALE for PMV patients was 9.87-10.17 QALY, corresponding to a health gap of 94-97% (Chapter 3).

The ICER for PMV varies greatly depending on different underlying causes and co-morbidities. Among these patients, maintenance treatments for PMV patients with poor cognition or patients more than 85 years of age might be the least cost-effective (Chapter 4).

Conclusion: Theses results of poor prognosis would provide stakeholders evidence for communication to facilitate clinical decisions. Moreover, the results can also serve as a starting point for a public dialogue on resource allocation of the NHI on critical care, aging and palliative care.

Key Words: respiratory care, life expectancy, incidence rate, co-nobilities, quality of life, quality-adjusted life expectancy, cost-effectiveness

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Appendix 2

Hung MC, Yan YH, Fan PS, et al. Estimation of quality-adjusted life expectancy in patients under prolonged mechanical ventilation. Value Health 2011; 14:347-53.

Appendix 3

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Overview

As we know, the core value of public health is health for all and the first step would be to achieve the goal of health care for all. In Taiwan, we are very fortunate to have developed the National Health Insurance (NHI) that implements a system of universal coverage (over 99% now) for all people of Taiwan. The NHI comprehensively covers various health care services, especially those of catastrophic illnesses, including maintenance hemodialysis for end stage renal disease and chronic ventilator use consecutively for more than 21 days, etc., which results in a tremendous financial burden and threatens the sustainability of the NHI. According to the reimbursement data of NHI in 2010, the prolonged mechanical ventilation (PMV) consumes the second highest in the average health expenditure with an annual total health expenditure of 17 billion NT (New Taiwan) dollars. In order to keep the sustainability of the NHI under good quality, efficiency and equitable distribution of resources at the same time, we began to think of different strategies. One of them is to explore the incidence rate, quality of life, and survival of the patient undergone prolonged mechanical ventilation, and cost effectiveness of such a healthcare service.

In 1998, the Bureau of NHI drafted a prospective payment program to encourage integrated care for mechanically ventilated patients, which was implemented in July 2000. After several revisions, this program ultimately covered four types of mechanical ventilator care: ICU care (acute stage, <21 days), respiratory care center (RCC, a sub-acute stage for weaning training of up to 42 days), respiratory care ward (RCW, a chronic stage or long-term care), and home care service (stable stage, in which the patient is cared for directly by family caregivers).

The number of patients who require PMV is rapidly increasing worldwide, apparently due to aging, a greater number of co-morbidities, and the increasing availability and effectiveness of this new technology. The fact that many patients require continued respiratory care after being transferred into a rehabilitation facility creates a tremendous financial burden. Furthermore, there is often a gap between families' unreasonably optimistic expectations and clinicians' professional judgment. This gap frequently results in difficulties arriving at consensus clinical decision-making. In many cases, these challenges are not easily resolved. These issues are exacerbated by the lack of evidence regarding expected survival times for different subgroups of patients, especially for those suffering from multiple co-morbidities.

The financial impact is particularly heavy for countries with a national health insurance system with universal coverage of their citizens and is aggravated by the innovation of new technologies and an aging population. Most of these countries have adopted economic analyses to improve overall cost-effectiveness and contain costs. Evaluation of the cost per QALY (quality-adjusted life year) gained from different healthcare services will ensure the most cost-effective policy decision for health care.

Similar to what is the case in western countries, discrepancies frequently exist in Taiwan between a family's initial expectations and their physician's professional judgment. These discrepancies impair communication among patients, their families, and health care workers for clinical decision-making before and throughout the course of installing mechanical ventilation. Thus, there is a need to estimate the incidence rates and life expectancies for PMV patients with various diagnoses. Accurate prognoses are essential to propose and establish a sustainable national policy and to facilitate communication among different stakeholders. To examine the above issues, we collected a random sample from the national database and compared age-specific incidence rates, cumulative incidence rates (CIRs), median survival, and life expectancies of PMV patients stratified according to their underlying diseases.

To our knowledge, there has been few study that estimates the long term survival, quality of life, lifetime cost, and cost effectiveness together for PMV patients with multiple co-morbidities, which are the major goals of this dissertation. The aims of our study are: (1) to determine the incidence rate (IR), median survival, life expectancies for different types or co-morbidities of patients undergoing prolonged mechanical ventilation (PMV) ; (2) to explore how much difference on the quality of life (QOL) assessments between patients under PMV and their proxies (family caregivers and nurses); (3) to estimate the quality-adjusted life expectancy (QALE) and the expected lifetime utility loss of different types of patients with PMV (4) and to estimate the incremental cost-effectiveness ratios (ICER) for different types of patients undergoing PMV.

To achieve these aims, together we have already performed the following four studies:

1. Life expectancies and incidence rates of patients under prolonged mechanical ventilation: A population-based study during 1998-2007 in Taiwan (Chapter 1)
2. Measurement of quality of life using EQ-5D in patients on prolonged mechanical ventilation: comparison of patients, family caregivers and nurses (Chapter 2)
3. Estimation of quality-adjusted life expectancy in patients under prolonged mechanical ventilation (Chapter 3)
4. Cost-effectiveness of applying prolonged mechanical ventilation in Taiwan (Chapter 4)

Life expectancies and incidence rates of patients under prolonged mechanical ventilation: A population-based study during 1998-2007 in Taiwan

(Chapter 1)

Abstract

Introduction: This study examined the median survival, life expectancies, and cumulative incidence rate (CIR) of patients undergoing prolonged mechanical ventilation (PMV) stratified by different underlying diseases.

Methods: According to the National Health Insurance Research Database (NHIRD) of Taiwan, there were 8,906,406 individuals who obtained respiratory care during the period from 1997-2007. A random sample of this population was performed, and subjects who had continuously undergone mechanical ventilation for more than 21 days were enrolled in the current study. Annual incidence rates and CIR were calculated. After stratifying the patients according to their specific diagnoses, latent class analysis (LCA) was performed to categorize PMV patients with multiple co-morbidities into several groups. The life expectancies of different groups were estimated using a semi-parametric method with a hazard function based on the vital statistics of Taiwan.

Results: The analysis of 50,481 PMV patients revealed that incidence rates increased as patients grew older and that cumulative incidence rates (17-85 years old) increased from 0.103 in 1998 to 0.183 in 2004 before stabilising thereafter. The life expectancies of PMV patients suffering from degenerative neurological diseases, stroke, or injuries tended to be longer than those with chronic renal failure or cancer. Patients with chronic obstructive pulmonary disease survived longer than did those co-morbid with other underlying diseases, especially septicaemia/shock.

Conclusions: PMV provides a direct means to treat respiratory tract diseases and to sustain respiration in individuals suffering from degenerative neurological diseases, and

individuals with either of these types of conditions respond better to PMV than do those with other co-morbidities. Future research is required to determine the cost-effectiveness of this treatment paradigm.

1.1 Introduction

The number of patients who require prolonged mechanical ventilation (PMV) is rapidly increasing worldwide, apparently due to aging, a greater number of co-morbidities, and the increasing availability and effectiveness of this new technology [1-3]. The fact that many patients require continued respiratory care after being transferred into a rehabilitation facility creates a tremendous financial burden [3-4]. Furthermore, there is often a gap between families' unreasonably optimistic expectations and clinicians' professional judgment. This gap frequently results in difficulties arriving at consensus clinical decision-making [5]. In many cases, these challenges are not easily resolved. These issues are exacerbated by the lack of evidence regarding expected survival times for different subgroups of patients, especially for those suffering from multiple co-morbidities.

The National Health Insurance (NHI) of Taiwan has implemented a system of comprehensive coverage for various health care services, including maintenance hemodialysis and chronic respiratory care. The NHI was first established in 1995 and has been extended to cover over 99% of the citizens of Taiwan [6-7]. In 1998, the Bureau of the NHI drafted a prospective payment program to encourage integrated care for mechanically ventilated patients, which was implemented in July, 2000 [8]. After several revisions, this program ultimately covered mechanical ventilator care in the following settings: intensive care units (ICU, acute stage, <21 days), respiratory care centres (RCC, a sub-acute stage for weaning training, up to 42 days), respiratory care wards (RCW, a chronic stage or long-term care), and home care services (a stable stage during which the patient is cared for directly by family caregivers). The rising number of patient-days for mechanical ventilation usage during 1997-2004 increased the financial burden of the NHI [9]. Similar to what is the case in Western countries [5], discrepancies frequently exist in Taiwan between a family's initial expectations and their physician's professional judgment. These discrepancies impair communication among patients, their families, and health care workers for clinical decision-making before and throughout the course of installing mechanical ventilation. Thus, there is a need to estimate the incidence rates and life expectancies for PMV patients with various diagnoses. Accurate prognoses are essential to propose and establish a sustainable national policy and to facilitate communication among different stakeholders. To examine the above issues, we collected a random sample from the national database and compared age-specific incidence rates, cumulative incidence rates (CIRs), median survival, and life expectancies of PMV patients stratified according to their underlying diseases.

1.2 Materials and methods

Study population, datasets, and calculation of age-specific and cumulative incidence rates

This study was approved by the Institutional Review Board of the National Taiwan University Hospital, which also waived the requirement for obtaining informed consent because the study was conducted on a secondary database with encrypted identification numbers. The reimbursement data file obtained from the NHI of Taiwan was transformed into a research database by the National Health Research Institutes (in Chunan, Taiwan) [10]. The identification numbers of all individuals in the reimbursement data file were encrypted to protect their privacy. These files contained detailed demographic data (including birth date and sex) and information regarding the health care services provided for each patient, including all payments for outpatient visits, hospitalizations, prescriptions, diagnoses and intervention procedures. The data for each inpatient hospitalization included up to five diagnoses, which were coded according to the International Classification of Diseases, Ninth Revision (ICD-9) and the date of each prescription or procedure. In total, 8,906,406 individuals had undergone invasive or non-invasive respiratory care at least once during the period from 1997-2007. This number corresponds to approximately 29.4% of the entire insured population. Because the government has established guidelines stating that no more than 10% of all data can be drawn for research, we applied for a random sample of these patients with a 3.4:1 ratio and enrolled subjects who had undergone mechanical ventilation for more than 21 days.

According to the definition of PMV in Taiwan [8], we included patients over the age of 17 who had undergone either invasive or non-invasive mechanical ventilation, with negative or positive pressure ventilators for at least 21 consecutive days in the ICU or the RCC. To ensure that all of the patients were incident cases, we excluded all prevalent cases found in 1997 and began the collection in 1998, as illustrated in Figure 1.1. The calendar year- and age-specific incidence rates (IRi) were determined by taking the number of new cases of PMV patients in that stratum, multiplying by the sampling factor of 3.4, and then dividing the resulting value by the number of individuals within the specific stratum obtained from the census of the Ministry of the Interior in Taiwan [11]. The CIR (cumulative incidence rate) formula was calculated as follows [12]: $CIR=1-\exp\,[-\Sigma i\ (IRi)\ (\triangle t_i\ )]$, where IRi represents the age-specific incidence rate and $\triangle t_i$ indicates the range of each age stratum. We calculated the $CIR_{17\text{-}85}$, which estimates the likelihood that an average person in Taiwan would require PMV assuming that he or she lives to the age of 85.

Categorization of patients for estimation of life expectancies

All recruited subjects were followed until the end of 2007 to determine whether they were alive, deceased, or censored. Because patients who had undergone PMV usually suffered from a combination of multiple co-morbidities and 5 major diagnoses can be retrieved for each PMV patient prior to and closest to the 1st day, we developed a strategy to identify different homogeneous groups to make more-accurate estimates of life expectancy. First, we excluded specific categories with extremely low frequencies, including HIV (human immunodeficiency virus) infection (n=27) and complications during pregnancy/childbirth/perinatal period (n=240). Second, people with major diagnoses that may cause premature mortality were stratified and analysed separately, including cancer, end-stage renal disease, liver cirrhosis, multiple sclerosis or degenerative neurological diseases, Parkinson's disease and injury or poisoning , as each group shares major common characteristics that predict mortality. Third, because the vast majority of patients suffered from a combination of multiple chronic diseases that may cause premature mortality, such as diabetes mellitus, coronary and/or heart failure, hypertension, respiratory system and/or urinary tract infections, acute renal failure, and septicaemia with and without shock, etc., we conducted latent class analysis for these cases to categorize them into clusters or specific homogeneous groups for estimations of life expectancies. During this process, we grouped several closely related diagnoses together and converted their original ICD-9 codes into Clinical Classifications Software (CCS) codes [13] so that sufficient numbers could be obtained for survival analysis. Following the above direction, the ICD-9 codes of septicaemia included 0031, 0202, 0223, 0362, all subcategories of 038, and 7907 (bacteraemia); those of shock included all subcategories under code 785.

Statistical analysis

Binary and categorical variables were summarized using frequency counts and percentages. Continuous variables that were distributed normally are presented as means.

Latent class analysis

To determine the underlying causes that were more likely to lead to PMV, we applied latent class analysis (LCA) to group separate co-morbidity diagnoses into no more than 10 clusters of in-patients who had undergone PMV. Because pneumonia and respiratory failure are the most common reasons for mechanical ventilation, these conditions were not included in this model. This analysis resulted in an LCA model consisting of 32 broad diagnosis categories that included chronic diseases that had been previously classified into 260 categories by CCS. LCA assumes that responses are conditionally independent within classes after accounting for class membership [14]. In other words, LCA allows for the grouping of the PMV patients into several relatively homogeneous clusters of diagnosis patterns. In constructing the model, each cluster or class was named after the major disease (*i.e.*, with the highest prevalence or likelihood) present within each age strata. Akaike Information Criteria (AIC) was used to assess the goodness of fit of the model [15]. Lower AIC statistics were considered to indicate a better statistical fit of the model to the data. If any single category exhibited a prevalence approaching 100% for a given condition across different age groups, then we assumed that these conditions could be re-classified into groups with specific diseases, and life expectancy estimations were conducted separately. Throughout this process, we found that only stroke could be further separated from the groups of multiple co-morbidities, and thus, the life expectancy estimation for stroke patients was performed independently. SAS statistical software (version 9.1) and R statistical software (version 2.10.1) were used for the data analyses.

Estimation of life expectancy

Each new patient who fulfilled the definition of PMV was followed beginning on the 1st day of PMV treatment and continuing until he/she was deceased or censored on December 31st of 2007. The median survival, or the time at which only half of the patients within a given category were still alive, was estimated by the Kaplan-Meier method. In general, most patients did not survive longer than 1-3 years, although some patients did exhibit a longer survival time. All patients survived the initial 21 days of treatment by mechanical ventilation, and the survival times reported here exclusively refer to survival duration thereafter. Thus, the lifetime survival of PMV patients (up to 300 months when excluding those older than 85 years) was obtained using a linear extrapolation of a logit-transformed curve of the survival ratio between the PMV and an age- and gender-matched reference population generated by the Monte Carlo method from the life table of the general population of Taiwan. The detailed method and mathematical proof assuming a constant excess hazard have been described in our previous reports [16-20]. To facilitate the computation, we used ISQoL, a software program that was built based on the *R* statistical package for lifetime expectancy estimation and 300-month extrapolation (excluding those older than 85 years) and can be downloaded for free [21].

Validation of the extrapolation method for survival functions

Empirical PMV data from the National Health Research Institutes provided us with an opportunity to validate the actual performance of our semi-parametric method of estimation. Thus, we selected sub-cohorts of patients beginning on the 1st day that they received PMV between 1998 and 2001. We assumed that these cohorts were only followed until the end of 2001 and then extrapolated these results to the end of 2007. We compared our predictions with the Kaplan-Meier estimates of the direct follow-ups from 1998-2007. Assuming that the Kaplan-Meier estimates are the gold standard, we calculated the relative biases for sub-cohorts stratified by different underlying diseases and co-morbidities [22]. The relative biases were computed to compare the differences in values between the Kaplan-Meier estimates and the Monte Carlo extrapolation method.

1.3 Results

Basic characteristics of the PMV Cohort

A total of 50,481 new patients with PMV were included during the study period (40% female, mean age of 72±14.5 years, median survival 0.37 years, and overall life expectancy of 2.68 years). If we counted only the primary diagnosis (out of a maximum of five diagnoses) for each patient, the top five primary diagnoses were acute respiratory failure (15%), pneumonia (12%), intra-cerebral haemorrhage (5%), septicaemia (3%) and chronic airways obstruction (2%). The tracheotomy rate was 60.1%, which reflects the ethnic Chinese cultural tradition that typically avoids additional traumatic wounds if a patient is expected to pass away soon.

Trends of age-specific incidence rates and CIR over time

After NHI began to reimburse long term usage of mechanical ventilation to relieve the congested intensive care ward in 1998, the incidence rate started to rise and showed an increased trend with older age (Table 1.1). In the groups aged 65-74, 75-84, and older than 85 years, increased incidence rates of 76%, 88%, and 119%, respectively, were observed from 1998 to 2004, followed by a slight drop after 2005. The CIR (17-85 years) increased from 0.103 in 1998 to 0.183 in 2004 and then decreased to 0.145 in 2007.

Life expectancies of PMV patients with specific underlying diseases

The median survival and life expectancies of PMV patients with different diseases are summarized in Table 1.2. Although median survival of most categories were less than one year, many patients showed life expectancies longer than 2-3 years, indicating that some patients survived relatively long periods of time. The median survival and life expectancies of PMV patients with degenerative neurological disease, stroke, or injuries were generally longer than those with chronic renal failure or cancer. When a patient contracted both cancer and chronic renal failure, the median survival durations and life expectancies were the shortest. Patients with stroke were initially included in the latent class analysis because of the presence of multiple co-morbidities, but a distinctive category of 100% prevalence of stroke consistently appeared across different age strata. Thus, we separated this group and estimated the associated life expectancies for different age strata, as summarized in Table 1.2.

Life expectancies of age-specific clusters in PMV patients with multiple co-morbidities

Among the 23,697 PMV patients with multiple co-morbidities, the latent class model usually yielded 3-4 clusters, including heart diseases, septicaemia/shock, chronic obstructive pulmonary diseases and/or others (e.g., urinary tract infections), as summarized in Table 1.3. Diabetes mellitus seemed to be the most frequent co-morbid disease among all different clusters because the prevalence rates were all above 14.5%. The life expectancy and median survival of PMV patients with COPD (chronic obstructive pulmonary disease) were generally longer than those of other clustered groups, especially those with septicaemia/shock. This trend continued until the age of 85, after which PMV patients with different underlying co-morbidities seem to show similar outcomes.

Validation results of the extrapolation method

The results obtained to validate our semi-parametric method show that the relative biases were all below 20%. Among them, the relative biases of most PMV patients with a specific diagnosis ranged between 0.9% and 5.5%. Stroke patients were an exception and usually suffered from other co-morbidities. Patients with a combination of different diseases (or clusters) appeared less likely to fulfil the assumption of a constant excess hazard completely and resulted in greater relative biases, perhaps because they represent a relatively heterogeneous patient population. Nonetheless, the absolute differences between our estimates and those obtained using the Kaplan-Meier method were all below 0.25 life-years, except for the 65-74-year-old multiple co-morbidity categories, which showed an absolute difference of 0.39 life-years.

1.4 Discussion

To our knowledge, this is the first study to analyze a nationally representative PMV dataset to estimate the incidence rates, CIR, and life expectancies stratified by age and different clusters of diagnoses. Our findings showed that new cases of PMV increased significantly from 9,296 to 21,818 between 1998 and 2004. The age-specific incidence rates increased as people grow older, a result that is consistent with previous reports from scholars in the U.S. and Canada [1-2, 4, 23]. However, the highest age-specific incidence rate of PMV was observed in patients older than 85 years in Taiwan, and this rate was approximately 4 to 5 times higher than those reported in the U.S. [24]. We attempted to quantify the lifetime risk of PMV by calculating the $\mathrm{CIR}_{17\text{-}85,}$ which increased from 0.103 to 0.145 between 1998 and 2007 (Table 1.1). This finding implies that an adult person in Taiwan who lives until the age of 85 has 10-15% chance of requiring PMV. Given the resource-intensiveness of PMV, this issue requires special attention. When the Bureau of National Health Insurance of Taiwan began to audit the quality of the integrated respiratory care system in 2003, including the rates of successful weaning, readmission and nosocomial infection, the incidence of PMV appeared to stabilize and decreased slightly, as summarized in Table 1.1.

In the past, there has been a general lack of data regarding the life expectancies associated with different diagnoses for patients undergoing PMV. This has made it difficult for stakeholders to reach consensus clinical decisions regarding optimal treatment strategies. The issue becomes even more complicated when payment is provided via NHI or a third party. It is understandable that the patient and his/her family always expect successful weaning and good recovery, even after more than 21 days of continuous mechanical ventilation or PMV. However, according to our previous study, most patients undergoing PMV survive only approximately 1.5 to 2 years, and approximately 62% of them suffer from cognitive impairments and poor quality of life. Accounting for these factors results in an overall quality-adjusted life expectancy of only 0.3-0.4 to 0.6-0.7 quality-adjusted life years (QALYs) [25-26]. Thus, this study further provided crucial estimates of the median survival and life expectancies of patients undergoing PMV with different diagnoses or co-morbidities, as summarized in Tables 1.2 and 1.3. Table 1.2 shows that the life expectancies were shortest for PMV patients with chronic renal failure and cancer or any condition co-morbid with them, followed by Parkinson's disease and stroke. In contrast, the life expectancies for degenerative neurological diseases, liver cirrhosis, injuries and poisonings were greater than 3.6 years. When stratified by age categories, the median survival and life expectancies for PMV patients older than 85 years were below 4.6 months and 21.8 months, respectively, which were also observed for all of the different types of co-morbidities (Tables 1.2 and 1.3). The above figures call into question the cost-effectiveness of current policies and should be considered by policy makers and the public in discussions regarding the bioethics of PMV care, especially given the limited resources of the NHI in Taiwan. Although more and more countries have tried to implement the principle of universal coverage in their national health insurance plans

[27], our results provide data highlighting the needed evidence for developing strategies of sustainable management.

Although previous studies have shown similar characteristics of multiple co-morbidities in PMV patients, these reports did not stratify patients into special clusters [1, 9, 24, 28]. The LCA showed that the underlying co-morbidities associated with PMV could be largely classified into the major categories of heart diseases, septicaemia/shock, and chronic obstructive pulmonary disease based on the high prevalence of each cluster. Overall, LCA indicates that the life expectancies generally decreased with older age. In particular, we found that approximately 50% of the PMV patients with a combination diagnosis of septicaemia and shock usually survived for less than 4 months, and their life expectancies were usually shorter than those determined for the other clusters within the same age stratum. The generally longer survival time of PMV patients with COPD corroborated the hypothesis that the establishment of mechanical ventilation provides more direct access for clinicians to solve problems coming from the respiratory tract, while patients with other underlying diseases may not be improved significantly unless their underlying disorders were also resolved. This advantage disappeared in individuals over 85 years of age because a high proportion of these COPD patients also suffered from other major diseases, including urinary tract infection (29%) and other respiratory diseases (26%), as shown in Table 1.3.

Our study has several limitations. First, the database did not contain any information regarding the severity and/or actual clinical data of the PMV patients. Thus, we were unable to further stratify these patients. However, because they were all under PMV care for more than 21 days, all of the patients were associated with extremely severe conditions, which resulted in a very short life expectancy and suggested that 10 years of follow-up time would be usually sufficient. Second, because the recorded diagnoses must fulfil all of the reimbursement regulations of the NHI, it is possible that some diagnoses are over-represented because they were more easily reimbursed. However, the National Health Insurance of Taiwan has offered a list of 30 major categories of catastrophic illnesses that are exempt from partial co-payments, and each has its specific diagnostic criteria to prevent any abuse [29]. For example, all types of malignant neoplasm do not require co-payments, and evidence of histopathology and/or cytology is generally required for diagnoses of cancer. A diagnosis of end stage renal disease requires documentation of chronic kidney disease with an irreversible creatinine level of more than 8 mg/dL, or creatinine level more than 6 mg/dL with diabetes mellitus as a co-morbid condition [30]. Thus, we have strict criteria for almost all the major diagnoses listed in Table 1.2. The potential selection bias for the common diseases listed in Table 1.3 is probably minimal because the 43 broad categories were collapsed from the 260 categories of CCS codes [13], and latent class analysis ensured that each category was as homogeneous as possible.

1.5 Conclusions

The number of PMV patients in Taiwan has increased during the last decade. Patients with different underlying diseases showed different median survival and life expectancies. The establishment of mechanical ventilation directly targets to solve problems of respiratory tract and provides sustainable ventilation, which may improve the survival of patients with COPD or degenerative neurological diseases more than those with other underlying causes such as septicaemia/shock, heart failure, cancer, or end stage renal disease. However, the advantages of PMV seem to decrease for the elderly, especially those over age 85. The results also call for further evaluation of the cost-effectiveness and bioethics of such care in Taiwan and highlight the need for early planning of resource allocation in any system of health insurance with universal coverage.

Key messages

- The number of new patients undergoing treatment of PMV (prolonged mechanical ventilation) has increased rapidly during the last decade in Taiwan.
- The life expectancies of PMV patients with degenerative neurological diseases, stroke, or injuries/poisoning as their primary co-morbidity seemed to survive longer than those with chronic renal failure or cancer, or a co-morbidity with them.
- Among PMV patients with multiple co-morbidities, those with COPD as the major underlying co-morbidity seem to survive longer than patients with other co-morbidities, perhaps because this treatment specifically targets the respiratory tract, which is compromised in COPD. The benefits of PMV decrease for the elderly, especially those with an age of over 85.

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Figure 1 Flow chart of the selection process used for the study cohort.

Table 1.1 Age-specific incidence rates (per 100,000 person-years), and CIR* of patients under prolonged mechanical ventilation

Age group, years	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
No. of new cases	9,296	12,651	12,913	15,660	17,731	19,737	21,818	21,692	20,414	19,723
17-34	5.1	6.1	5.5	5.8	6.1	8.4	9.9	9.2	9.4	9.9
35-44	10.1	10.8	11.8	14.5	14.4	15.4	19.2	17.4	19.8	18.1
45-54	21.8	33.3	29.3	32.4	37.2	42.0	40.5	43.5	39.5	39.7
55-64	78.2	101.1	92.2	102.5	111.6	118.9	129.6	119.8	101.7	93.0
65-74	224.0	296.5	284.5	329.2	361.9	379.8	393.9	369.2	331.8	306.4
75-84	622.0	817.2	814.6	967.2	1,045.5	1,072.3	1,166.4	1,036.0	1,004.6	909.2
≧85	1,182.0	1,536.0	1,702.6	2,064.1	2,253.0	2,563.9	2,584.0	2,554.0	2,161.0	2,046.0
CIR (17-85 yrs)	0.103	0.133	0.132	0.153	0.165	0.173	0.183	0.170	0.159	0.145

*CIR: cumulative incidence rates (aged 17-85 years old)

Table 1.2 Demographic characteristics and survival of patients undergoing prolonged mechanical ventilation stratified by different underlying diseases

	Number of cases	Mean age (SD)*	Female (%)	Median survival (yrs)	Life expectancy (yrs) (SE)*
Cases with single specific disease	21,316	69 (15)	38	0.35	3.40 (0.09)
Cancer	5,367	70 (14)	33	0.17	1.51 (0.13)
Chronic renal failure	2,032	73 (12)	51	0.78	1.36 (0.16)
Liver cirrhosis	1,478	65 (17)	35	0.19	3.59 (0.33)
Multiple sclerosis or degenerative nervous system conditions	378	65 (17)	39	0.89	4.05 (0.64)
Parkinson's disease	341	79 (7)	36	0.85	2.06 (0.30)
Stroke	6,765	70 (13)	42	0.72	3.38 (0.15)
<64 yrs	1,955	53 (9)	35	1.65	5.21 (0.39)
65-74 yrs	1,818	70 (3)	43	0.77	2.98 (0.17)
75-84 yrs	2,176	79 (3)	44	0.56	2.09 (0.13)
>85 yrs	816	88 (3)	54	0.39	1.68 (0.13)
Intracranial and/or spinal cord injury or poisoning	4,955	65 (19)	34	1.06	6.27 (0.24)
<64 yrs	1,949	45 (14)	26	6.20	10.20 (0.49)
65-74 yrs	1,116	70 (3)	39	0.82	3.77 (0.22)
75-84 yrs	13,66	79 (3)	35	0.47	2.67 (0.19)

>85 yrs	524	88 (3)	48	0.33	1.82 (0.13)
Cases with more than two specific diseases	4,772	68 (15)	39	0.32	2.96 (0.13)
Cancer and Chronic renal failure	165	71 (11)	44	0.14	1.21 (0.45)
Cancer and others	1,609	70 (14)	35	0.19	1.88 (0.22)
Chronic renal failure and others	743	70 (13)	50	0.21	1.71 (0.28)

* SD: standard deviation; SE: standard error of the mean

Table 1.3 Clusters of different co-morbidities categorized by latent class analysis in patients with prolonged mechanical ventilation

	<64 yrs (n= 3,520)				65-74 yrs (n= 5,397)			75-84 yrs (n= 9,747)				>85 yrs (n= 5,033)		
	Class 1 Heart diseases	Class 2 SP/ shock	Class 3 UTI/ SP	Class 4 COPD/ others	Class 1 Heart diseases	Class 2 SP/ shock	Class 3 COPD/ others	Class 1 Heart diseases	Class 2 SP/ shock	Class 3 COPD/ others	Class 4 Respiratory diseases	Class 1 Heart diseases	Class 2 SP/ shock	Class 3 COPD/ others
Number of cases	616	919	197	1,788	1,074	1,824	2,499	1,404	2,856	4,142	1,345	870	1,359	2,804
Prevalence of co-morbidity (%)														
Septicaemia	11.3	62.9	72.2	6.7	10.6	66.1	5.5	11.8	72.8	11.0	7.2	10.2	79.1	11.7
Diabetes mellitus	35.5	26.8	26.1	19.7	39.7	26.1	26.5	27.1	20.5	22.6	17.2	18.6	14.5	14.6
Hypertension	17.9	4.9	9.8	8.3	20.8	6.8	13.9	16.1	4.8	17.3	12.5	15.4	3.3	15.2
AMI/Coronary atherosclerosis	39.9	3.9	2.3	2.4	43.9	4.6	5.2	42.8	5.5	6.6	4.0	42.8	5.6	4.0
COPD	6.5	3.2	0.5	17.9	11.0	11.0	33.9	18.2	12.4	39.6	29.6	24.9	12.7	33.0
Other respiratory diseases	21.8	23.7	13.8	30.1	22.3	18.1	26.7	20.9	17.2	0	100	24.6	19.4	25.9
Acute renal failure	12.2	20.6	9.5	4.8	12.7	16.4	4.5	12.1	16.7	4.2	5.3	8.7	15.2	5.6
UTI	5.3	0	100	14.8	5.7	25.1	21.1	11.7	28.0	24.3	21.1	16.1	30.6	29.0
Shock	11.2	39.6	33.1	2.7	10.3	39.1	2.7	8.9	38.5	4.9	3.7	7.3	41.6	5.0
Heart failure	42.2	3.2	2.6	2.4	37.0	5.8	4.8	50.1	7.2	7.7	7.4	50.5	8.3	7.7
Median survival	0.80	0.34	0.88	1.64	0.39	0.23	0.55	0.29	0.21	0.95	0.38	0.32	0.20	0.35

(yrs)														
Life expectancy (yrs)	5.09	4.51	4.82	5.25	2.55	2.14	2.56	1.86	1.66	2.12	2.18	1.48	1.12	1.52
(SE)	(0.60)	(0.49)	(1.49)	(0.37)	(0.21)	(0.13)	(0.13)	(0.23)	(0.10)	(0.07)	(0.17)	(0.12)	(0.07)	(0.05)

COPD: chronic obstructive pulmonary disease; UTI: urinary tract infections; AMI: acute myocardial infarction; SP: septicaemia; SE: standard error of the mean

Measurement of quality of life using EQ-5D in patients on prolonged mechanical ventilation: comparison of patients, family caregivers and nurses

(Chapter 2)

Abstract

Purpose: This study reports how QOL (quality of life) assessments differ between patients on prolonged mechanical ventilation (PMV) and their proxies (family caregivers and nurses).

Methods: We enrolled consecutive subjects on PMV for more than 21 days from five institutions. We conducted QOL assessments using the Taiwanese version of the EQ-5D in face-to-face interviews. Direct caregivers (family members and nurses) also completed the EQ-5D from the patient's point of view.

Results: For 55 of the 142 enrolled patients who were able to assess their QOL, we recruited 44 patient-family caregiver pairs, 53 patient-nurse pairs, and 42 family caregiver-nurse pairs. There were 81 family caregiver-nurse pairs out of 87 patients with poor cognition. The agreement between patient-family caregiver pairs was generally higher than that of patient-nurse pairs. As the proportions of exact agreement between family caregivers and nurses for patients with poor cognition were 98-99% for observable dimensions of mobility, self-care, and usual activities, they lead to a minimal difference in the final values.

Conclusions: QOL assessments from family caregivers agreed more closely with patients than did those from nurses using EQ-5D evaluations for patients with clear cognition, but either proxy was acceptable for rating PMV patients with poor cognition.

2.1 Introduction

Patients who require prolonged mechanical ventilation (PMV) are rapidly increasing in number, as the improved quality of care in ICUs (intensive care units) has resulted in long-term survival for many patients [1-2]. However, these patients often require continued respiratory care after transfer to a rehabilitation facility, skilled nursing facility or home care, creating financial burdens for the insurance system and/or the patients' families [1, 3]. Several studies have reported [1, 4-6], however, that survivors often feel their quality of life (QOL) to be acceptable.

The National Health Insurance (NHI) of Taiwan uses a system of comprehensive coverage for various health care services, including maintenance hemodialysis and chronic respiratory care. The NHI was first established in 1995 and has been extended to cover over 99% of Taiwanese citizens [7-8]. In 1998, the Bureau of NHI drafted a prospective payment program to encourage integrated care for mechanically ventilated patients, which was implemented in July 2000 [9]. After several revisions, this program ultimately covered four types of mechanical ventilator care: ICU care (acute stage, <21 days), respiratory care center (RCC, a sub-acute stage for weaning training of up to 42 days), respiratory care ward (RCW, a chronic stage or long-term care), and home care service (stable stage, in which the patient is cared for directly by family caregivers).

Unlike patients on PMV in other countries [10-14], many patients in Taiwan suffer from concomitant cognitive impairments that preclude direct assessment of their subjective QOL, making evaluation by proxy unavoidable in many cases. The objective of this study was to evaluate the utility assessment of QOL in patients on PMV and to compare patients' own QOL assessments with those made on their behalf by proxies (family caregivers and professional nurses).

2.2 Material and methods

Subjects and Methods

We recruited subjects from five institutions in northern and southern Taiwan and consecutively enrolled current PMV subjects who had already been on mechanical ventilation for at least for 21 days at various levels of care (ICU, RCC and RCW): 1 medical center, 1 regional hospital, and 3 small local hospitals were included. The study began after approval was obtained from the Institutional Review Boards (IRBs) of the National Taiwan University Hospital and the Chia-Yi Christian Hospital. The three local hospitals also approved the study after reviewing the approval documents of the two major IRBs above. For subjects with basic cognition who were able to communicate (including through clear body language) and who scored at least 15 on the mini-mental status examination (MMSE) [15], we conducted QOL measurements using the EQ-5D in direct, face-to-face interviews. The primary caregivers (family members and nurses) were also asked to independently complete the EQ-5D questionnaire from the patient's point of view, i.e., each proxy rated how he or she thought the patient would rate his or her own QOL on the day of the interview. All the interviews with the patient and his/her proxy were required to be finished within three days, and we also made sure that the individual patient's clinical condition was stable by verifying with the medical records. The proxy's results were directly compared with the patient's own rating, which was considered to be the gold standard.

Quality of life measured by EQ-5D

The utility value of the QOL for patients on PMV was estimated using the EuroQol five-dimensional (EQ-5D) questionnaire, a generic preference-based instrument. The five dimensions assessed by the EQ-5D are mobility, self-care, usual activities, pain/discomfort and anxiety/depression, with three levels of severity (no problems, some/moderate problems and severe/extreme problems). This provides a utility value that ranges from 0 to 1 based upon the five-dimensional health state classification, in which 0 represents the worst health status and 1 represents perfect health [16-17]. The EQ-5D instrument is a valid and reliable tool for measuring health status that has been extensively used in many countries as an outcome measure, including for critically ill patients [18-20]. It was also recently applied in Taiwan with good validity and moderate reliability [21]. We applied the value systems of the U.S. and the U.K. as a comparison [17, 22]. There is general agreement that patients are the best raters of their QOL; however, when a patient's mental status is too poor, family caregivers and nurses may be considered as proxies [11-13]. QOL assessment by EQ-5D was conducted by three research assistants who were first trained in the standard operating procedure. For each patient and his/her proxy, the researcher recorded characteristics including age, gender, education, marital status, relationship to the patient, whether or not the proxy lived with the patient, frequency of caring for the patient, location (ICU or RCC or RCW), Glasgow Coma Scale (GCS), presence/absence of tracheotomy and duration of mechanical ventilation, and history of depression. The duration-to-date for each measurement was defined as beginning on the first day after PMV and ending on the date of interview by our researcher.

Statistical Analysis

Binary and categorical variables were summarized using frequency counts and percentages. Continuous variables are presented as means if normally distributed. The agreement between QOL scores from patients, family caregivers and nurses for each dimension was determined for each pair by calculating weighted kappa scores [23]. To evaluate any systematic tendency for proxy respondents to overestimate or underestimate QOL, we computed the patient-proxy and proxy-proxy mean differences in the final utility value of the EQ-5D. The mean difference between pair-scores and values were tested with the rank sum and paired-t tests to detect any significant difference when the sample size is small. We calculated the effect size by dividing the mean patient-proxy difference by the standard deviation of the patient responses. The magnitude of the standardized difference can be interpreted as follows: |*d*|=0.2, a small difference; |*d*|=0.5, a moderate difference; and |*d*|=0.8, a large difference [24]. The agreement between patients and proxies of the EQ-5D's summary index was assessed with one- way intra-class correlation coefficients (ICC) [25-26]. An ICC or weighted kappa less than 0.4 was considered to indicate poor agreement, 0.40-0.75 indicated moderate to good agreement, and values >0.75 indicated excellent agreement [23, 27-29]. Because the group was homogeneous in disease status and marginal distribution, the statistical ICC and weighted kappa underrate agreement [30]. Thus, we calculated the proportion of exact agreement, defined as the number of same response categories chosen between the index subject and the proxy divided by the total number of rating pairs [31].

2.3 Results

Basic characteristics of respondents

A total of 177 patients were invited for this study; 142 patients accepted interviews producing a response rate of 80%, as summarized in Figure 2.1. For the 55 patients able to assess their own QOL we collected 44 patient-family caregiver pairs, 53 patient-nurse pairs and 42 family caregiver-nurse pairs. We successfully collected 81 family caregiver-nurse pairs for 87 patients who were unable to assess their own QOL. We were unable to recruit any proxy for six patients with poor cognition.

The first proxy group (family caregivers) consisted of 129 persons; 57% were the patients' children, 58% lived with the patients, and 67% contacted the patients every day. The second proxy group (nurses) consisted of 135 persons, 27% of whom were directly responsible for the patients' everyday care (Table 2.1).

Agreement in each dimension

Although the weighted kappa scores indicated poor to moderate agreement (0.21-0.58) in the observable dimensions (mobility, self-care and usual activities) and poor agreement (0.00-0.35) in the subjective dimensions (pain/discomfort and anxiety/depression); the proportions of exact agreement were more than 75% and 28% for observable and subjective dimensions, respectively, indicating high agreement on the former dimension for both family caregivers and nurses (Table 2.2). Family caregivers in particular displayed better agreement with the patients compared to nurses on subjective feelings of pain/discomfort and anxiety/depression. In patients with poor cognition, the proportions of exact agreement of family caregiver-nurse pairs were all above 98% in the observable dimensions but only 37%-38% in the subjective dimensions (Table 2.3).

Agreement of EQ-5D Index

The mean EQ-5D Index among the 55 patients was 0.23±0.20. The mean differences in the EQ-5D Index were -0.03 ±0.14 and 0.03±0.22 for patient-family caregiver pairs and patient- nurse pairs, respectively; this difference was not statistically significant (Table 2.4). In PMV patients with poor cognition, the average EQ-5D Index assigned by family caregivers and nurses were 0.12±0.10 (0-0.44) and 0.14±0.11 (0-0.63), respectively. The effect size of the mean differences for these measurements was 0.13, which is small [24]. The ICC of the EQ-5D Index for patient-family caregiver pairs was excellent (0.76), which seems much higher than that of the patient-nurse pairs (0.36) (Table 2.4).

2.4 Discussion

To our knowledge, this study is the first that validates agreement on QOL between PMV patients and their proxies (family caregivers and nurses) as measured by the EQ-5D preference instrument; in addition, these conclusions were validated in both PMV patients with good and poor cognition. Our findings demonstrate that family caregivers tended to rate all dimensions as being more severe than did patients themselves and that family caregivers' assessments were in closer agreement with patients' assessments than were those of their nurses, using either observable dimensions or subjective feelings. Moreover, agreement on the observable dimensions between family caregivers and nurses was higher (proportions of exact agreement=98-99%) in PMV patients with poor cognition.

Our study corroborates previous investigations finding better agreement between patients and their proxies for directly observable dimensions (mobility, self-care and usual activities) than for assessments of subjective feelings and mental health (pain/discomfort and anxiety/depression) [32-34]. However, family caregivers tended to rate all dimensions at a slightly higher severity than did patients themselves, while nurses gave less severe ratings compared to patients (Table 2.2). Family caregivers were generally allowed to stay with patients after their hospitalization in RCW institutions, which may partially explain why they were apparently able to perceive so accurately the feelings of PMV patients, with all proportions of the exact agreement above 86% for observable dimensions and 52% for subjective dimensions. In addition, no significant differences were identified between the final EQ-5D utility values from the patient-family caregiver pairs (Table 2.4). In contrast, only 27% of the interviewed nurses had daily contact with the patients, as they generally rotated and took days off each week (Table 2.1). We applied multiple regression analysis to estimate the potential effect of this determinant on the mean difference between patient-nurse pairs, but it did not show any statistical significance. Overall, the agreement within patient-family caregiver pairs is consistently closer than that of patient-nurse pairs, indicating that family caregivers may be a more suitable proxy for PMV patients in the Taiwanese culture.

In PMV patients with poor cognition, it is not surprising that both the weighted kappa (Table 2.3) and ICC (Table 2.4) were very low, because these patients were generally bed-ridden in RCC/RCW units and there is almost zero variation in the observable dimensions of mobility, self-care, and usual activities. Thus, such extremely limited distributions hamper the values of weighted kappa and ICC, and we must also provide the results of proportions of exact agreement, which were as high as 37-99% (Table 2.3) to avoid misinterpretation.

Nonetheless, there was no statistically significant difference between the final utility values of EQ-5D from patient-family caregiver and patient-nurse pairs in PMV patients with partial cognition. Because the EQ-5D value system of Taiwan has not yet been published, we applied the values obtained from the U.S. and U.K. for sensitivity analysis [17, 22]. Although the values based on the U.S. system seem smaller than those from the U.K., they yielded similar results, apparently due to the limited variation of health states in these patients (Table 2.4). Thus, the nurse's rating appears as acceptable as that of a family caregiver for use as a proxy to rate the utility value of the EQ-5D in PMV patients with poor cognition, even though the ICC of these pairs was only 0.00.

A possible limitation of this study was its cross-sectional design. Although we conducted a multiple regression analysis using the utility value of EQ-5D as the dependent variable and the duration of mechanical ventilation as an independent variable in the model, there was no significant difference. Thus, we were unable to answer whether the agreement of QOL measurements between patients and proxies may change longitudinally over different time points. Another possible limitation was the 80% response rate and the degree to which our sample was representative of the population as a whole. There was no statistically significant difference in patient characteristics between respondents and non-respondents. However, because family members of 22 of the 35 non-respondents did not come to visit the patients during our 3 to 4week study period, those patients might have a poorer QOL compared to that of the others. Ten family caregivers refused to be interviewed at the time of our request, as they were coping with their relative’s deteriorating condition. Thus, our results might have over-estimated the QOL of PMV patients. Finally, the extremely skewed responses in the objective dimensions of the EQ-5D in patients with poor cognition result in a generally low weighted kappa (Table 2.3), reflecting the inappropriateness of using such indicators. Thus, we have calculated the proportion of agreement to allow us to make a suitable inference.

2.5 Conclusions

Although the sensitivity analysis did not show any significant differences in overall utility value of QOL measurements using EQ-5D between patients on PMV and their proxies, family caregivers exhibited closer agreement with the patients than did nurses on QOL evaluation, especially on rating subjective feelings of pain/discomfort and anxiety/depression. However, there was no difference between the two proxies in the final utility values for PMV patients with poor cognition. Further research into these issues is still needed in subjects from different cultures to corroborate our findings.

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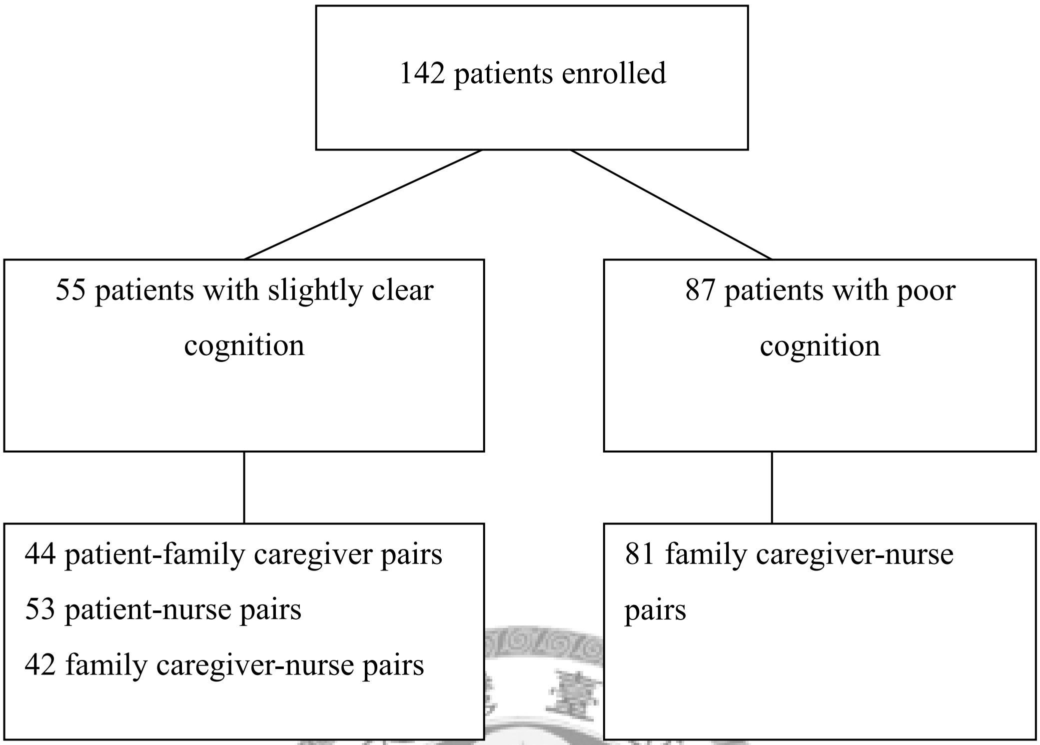

Figure 2.1 Recruitment process for study participants

Table 2.1 Characteristics of study subjects and proxies (family caregivers and nurses). Values are expressed as means (standard deviations) or percentages.

Characteristics	Patients	Family caregivers	Nurses
Total number of subjects	55	129	135
Mean age in (years) (S.D.)	70.9 (13.2)	51.5 (11.7)	27.7 (3.6)
% Females	49	46	95
% Above junior high school education	31	56	98
% Married	96	-	-
Relationship with the patient			
% Spouse	-	26	-
% Child	-	57	-
% Others	-	17	-
% Living together	-	58	-
% Frequency of contact with patient			
Daily	-	67	27
>once a week	-	25	54
< once a week	-	8	19
Glasgow Coma Scale (S.D.)	9.9 (2.5)	-	-
% Tracheotomy	71	-	-
Duration of mechanical ventilation (months)	19.1(26.0)	-	-

Table 2.2 Frequency distribution of agreement among patients with fair to good cognition (mini-mental status examination score >15) for each dimension of the EQ-5D.

Dimension	Patient n=55 (%)	Family caregiver n=44 (%)	Nurse n=53 (%)	Patient-Family caregiver n=44 weighted Kappa (confidence intervals) and [proportion of exact agreement]	Patient -Nurse n=53 weighted Kappa (confidence intervals) and [proportion of exact agreement]
Mobility					
No problems	0	0	2 (4)		
Problems	11 (20)	8 (18)	10 (19)	0.58 (0.28-0.88)	0.28 (0.01-0.55)
Confined to bed	44 (80)	36 (82)	41 (77)	[86%]	[75%]
Self-Care					
No problems	0	0	0		
Some problems	8 (15)	3 (7)	11 (21)	0.56 (0.19-0.93)	0.21 (-0.11-0.52)
Unable to wash/dress	47 (85)	41 (93)	42 (79)	[91%]	[77%]
Usual Activities					
No problems	0	0	1 (2)		
Some problems	11 (20)	7 (16)	11 (21)	0.44 (0.09-0.79)	0.26 (-0.03-0.56)
Unable to perform	44 (80)	37 (84)	41 (77)	[91%]	[75%]
Pain/Discomfort					
None	20 (36)	10 (23)	8 (15)		
Moderate	17 (31)	19 (43)	38 (72)	0.35 (0.13-0.57)	0.00 (-0.17-0.16)
Extreme	18 (33)	15 (34)	7 (13)	[52%]	[28%]
Anxiety/Depression					
None	27 (50)	13 (30)	7 (13)		
Moderate	14 (25)	13 (30)	36 (68)	0.35 (0.13-0.57)	0.18 (0.01-0.34)
Extreme	14 (25)	18 (40)	10 (19)	[52%]	[38%]

Table 2.3 Frequency distribution of agreement among patients with poor cognition and their proxies for each dimension in the EQ-5D.

Dimension	Family caregiver n=81 (%)	Nurse n=81 (%)	Family caregiver-Nurse n=81 weighted Kappa (confidence intervals) and [proportion of exact agreement]
Mobility			
No problems	0	0	
Problems	1 (1)	1 (1)	-0.01 (-0.03-0.00)
Confined to bed	80 (99)	80 (99)	[98%]
Self-Care			
No problems	0	0	
Some problems	0	1 (1)	0.00 (-0.00-0.00)
Unable to wash/dress	81 (100)	80 (99)	[99%]
Usual Activities			
No problems	0	0	
Some problems	0	1 (1)	0.00 (-0.00-0.00)
Unable to perform	81 (100)	80 (99)	[99%]
Pain/Discomfort			
None	16 (20)	9 (11)	
Moderate	27 (33)	45 (56)	0.05 (-0.13-0.23)
Extreme	38 (47)	27 (33)	[37%]
Anxiety/Depression			
None	19 (23)	10 (12)	
Moderate	30 (37)	48 (59)	0.08 (-0.08-0.24)
Extreme	32 (40)	23 (28)	[38%]

Table 2.4 Differences and reliabilities of EQ-5D index measured in patients on PMV (prolonged mechanical ventilation) and their proxies, according to value systems established in the United Kingdom (U.K.) and United States (U.S.).

	Mean difference [a,b] ±SD (minimum-maximum)		Effect size		ICC [c.d] (confidence intervals)
	U.S.	U.K.	U.S.	U.K.	
Patients with partial cognition capable of responding (Mini-Mental Status Exam, MMSE≧15)					
Patient-family caregiver (n=44)	-0.03±0.14 (-0.52-0.22)	-0.04±0.17 (-0.39-0.37)	0.21	0.24	0.76 (0.60-0.86)
Patient-nurse (n=53)	0.03±0.22 (-0.60-0.50)	0.00±0.23 (-0.51-0.46)	0.14	0.00	0.36 (0.11-0.58)
Family caregiver-nurse (n=42)	0.07±0.18* (-0.38-0.40)	0.07±0.22* (-0.44-0.50)	0.39	0.32	0.49 (0.22-0.69)
Patients with poor cognition and unable to respond (MMSE<15)					
Family caregiver-nurse (n=81)	0.02±0.15 (-0.38-0.52) [e]	0.02±0.20 (-0.37-0.44) [e]	0.13	0.10	0.00 (-0.22-0.20)

[a] Proxy minus patient score: A negative sign indicates that proxies underestimated the score.

[b] Nurse minus family caregiver: A negative sign indicates that the nurses consistently scored lower than did family caregivers.

[c] ICC: intra-class correlation coefficients

[d] U.S. value system only

* p<0.05

Estimation of quality-adjusted life expectancy in patients under prolonged mechanical ventilation

(Chapter 3)

Abstract

Objectives: The purpose of this study was to estimate the quality-adjusted life expectancy (QALE) and the expected lifetime utility loss of patients with prolonged mechanical ventilation (PMV).

Methods: PMV was defined as more than 21 days of mechanical ventilation. A total of 633 patients fulfilled this definition and were followed for nine years (1998-2007) to obtain their survival status. Quality of life of 142 patients was measured with the EQ-5D questionnaire during 2008-2009. The survival probabilities for each time point were adjusted with a utility measurement of quality of life and then extrapolated to 300 months to obtain the QALE. Further, we compared the age-, gender-matched reference populations to calculate the expected lifetime utility loss.

Results: The average age of subjects was 76 years old. The life expectancy and loss of life expectancy were 1.95 years and 8.48 years, respectively. The QALE of 55 patients with partial cognitive ability and the ability to respond was 0.58 quality-adjusted life years (QALY), whereas the QALEs of 87 patients with poor consciousness were 0.28 and 0.29 QALY for the EQ-5D measured by family caregivers and nurses, respectively. The loss of QALE for PMV patients was 9.87-10.17 QALY, corresponding to a health gap of 94-97%.

Conclusions: Theses results of poor prognosis would provide stakeholders evidence for communication to facilitate clinical decisions. The estimation may be used in future studies to facilitate the cost-effectiveness and reduction of the health gap.

3.1 Introduction

The number of patients requiring prolonged mechanical ventilation (PMV) is rapidly increasing, as the improved quality of care in ICUs (intensive care units) has resulted in the long term survival of many patients [1-3]. However, these patients often continually require respiratory care after transfer into a rehabilitation facility, skilled nursing facility or home care, which creates tremendous financial burdens to the insurance system and/or their families [2-3]. The financial impact is particularly heavy for countries with a national health insurance system with universal coverage of their citizens and is aggravated by the innovation of new technologies and an aging population [4]. Most of these countries have adopted economic analyses to improve overall cost-effectiveness and contain costs [5-7]. Evaluation of the cost per QALY (quality-adjusted life year) gained from different healthcare services will ensure the most cost-effective policy decision for health care.

The National Health Insurance (NHI) of Taiwan adopts a system of comprehensive coverage for various health care services, including maintenance hemodialysis and chronic respiratory care. It was first established in 1995 and has been extended to cover over 99% of the citizens of Taiwan [8-9]. The NHI has established a Pilot Program of Ventilator Dependent Managed Care in 2002 to provide subsequent and long term care for patients using PMV who are overcrowding the ICU. The program intended to cover medical services in the acute stage in the ICU, during weaning trials in the RCC (respiratory care center), dispatch to the RCW (respiratory care ward) if weaning trials failed, and respiratory therapy in home care. As the expense of chronic care for patients under PMV at home is generally too profound for most families, many try to keep their loved ones at the RCW for as long as possible. Thus, the reimbursement has resulted in a large financial burden to the NHI. During 2005, the total number of PMV patients that require respiratory care in the NHI of Taiwan has reached 30,000 and has accounted for

7.5% of the total NHI health care expenditures, which has become one of the major threats to the sustainability of the NHI [10-11].

To our knowledge, no study has considered both long term survival and quality of life together for PMV patients. Such a lack of prognostic data plus the families' unreasonably optimistic expectations often complicates the family-physician interaction [12], and makes it difficult to communicate among patients, their families, and health care workers for clinical decision making before and throughout the course of installing mechanical ventilation. Therefore, the purpose of this study was to estimate the QOL utility, lifetime survival, quality-adjusted life expectancy (QALE), and expected utility loss for patients using PMV.

3.2 Material and methods

The cohort and survival of PMV patients

We recruited all patients who were admitted to the intensive care unit and later received care at an RCC and RCW in a teaching hospital in southern Taiwan between 1998 and 2007. The recruitment criterion for PMV patients was the need for mechanical ventilation support for more than 6 hours per day for 21 days [13]. Each patient was followed from the 22nd day that he/she received PMV until he/she was deceased or censored on December 31, 2007. The Kaplan-Meier method was applied to estimate the survival function.

In general, when the patients are unable to have a normal respiration function, mechanical ventilation is installed for the support of life. It is commonly established in the intensive or critical care unit, and usually need to be performed tracheotomy to provide a consistently patent airway. Even under the ventilator support, such patients did not survive for more than 1-3 years, but occasionally there were patients with a longer survival. Thus, lifetime survival of PMV patients (up to 300 months) was obtained using a linear extrapolation of a logit-transformed curve of the survival ratio between the PMV and an age-, gender- matched reference population generated by the Monte Carlo method from the life table of the general population of Taiwan. The detailed method and the mathematical proof under the assumption of constant excess hazard can be found in our previous reports [14-18] and are briefly summarized below. Because the collection period of PMV patients ranged from 1998-2007, we chose the life table of the middle year (2002) for the Monte Carlo simulation.

Survival function of the age-, gender- matched hypothetical reference population

The life tables for the general population were obtained from the vital statistics, as published by the Department of Statistics, Ministry of the Interior, Executive Yuan, Taiwan [19]. Because the individual survival time of the subjects in a hypothetical cohort cannot be directly derived from the life table of the general population, we used the Monte Carlo method to generate the simulated survival time of age- and sex-matched hypothetical reference subjects for each patient in the PMV cohorts. The total collection of hypothetical subjects was used as the reference population. Then, the survival curve of the reference population was obtained by applying the Kaplan–Meier method to the simulated survival times.

Cross-sectional sample of PMV patients for utility measurements of QOL

To estimate the QOL utility function for these patients, we recruited a cross sectional sample of PMV subjects [18] who, after 21 days, continued to receive care from five institutions in Taiwan. Informed consent was obtained from every patient and/or his/her family caregiver, and the study commenced after the approval of the Institutional Review Boards (IRBs) of Chia-Yi Christian Hospital and National Taiwan University Hospital. The three local hospitals also approved the study after reviewing the approval documents of the above two major IRBs.

The utility value of the QOL for PMV patients was measured using the EuroQol five-dimensional (EQ-5D) questionnaire, which is a preference-based, generic instrument [20-21], and has been extensively used in many critically ill patients based on multi-attribute utility theory [22-24]. The five dimensions assessed by the EQ-5D are mobility, self-care, usual activities, pain/discomfort and anxiety/depression, each with three levels of severity (no problems, some/moderate problems and severe/extreme problems). This provides a utility value that ranges from 0 to 1 based upon the five-dimensional health state classification, in which 0 represents the worst health status and 1 represents perfect health. For subjects with basic cognition who communicated their responses and achieved a score of more than 15 on a mini-mental state examination (MMSE) [25-26], we conducted QOL measurements with the EQ-5D via direct face-to-face interview. Each individual patient was cross-sectionally measured one time on EQ-5D. When the patient's consciousness was too poor to communicate with the interviewer, family caregivers and nurses were used as proxies [27-30]. We have summarized the detailed methods of validating measurements in another study [31]. Briefly, we invited both family caregivers and nurses who directly took care of the patient to also evaluate the five dimensions of EQ-5D on the patient's behalf based on his/her understanding. The results were directly compared with the patient's own rating, which is considered the gold standard. The duration-to-date for each measurement is defined from the 22nd day after PMV to the date of the interview by the researcher; a cross sectional sample of patients with PMV was obtained, of which the kernel-type smoothing method (moving average of the nearby 10%) was performed to calculate the mean QOL throughout the follow-up time period of 9 years [17, 18]. The QOL value after 9 years was assumed to be the same as the end of follow-up time. We compared our results with the value systems of the U.S. and the U.K. [21, 32].

Statistical Analysis

*Integration of survival and QOL functions, QALE, lifetime utility loss, and health ga*p

The lifetime survival probabilities along the duration-to-dates (or time after beginning PMV) were multiplied (or adjusted) with the QOL values measured from EQ-5D to obtain a quality-adjusted survival curve, of which the sum of the total area under this curve was the QALE (quality-adjusted life expectancy) with QALY as the common unit [18]. The expected lifetime utility loss for PMV patients was calculated by assuming a uniform utility of one for the age- and gender- matched reference subjects and subtracting the QALE of PMV patients [14, 16, and 18]. In other words, based on the hazard function or vital statistics of Taiwan, we simulated survival functions of 10 reference people of the same age and gender for every PMV patient, and assumed that the utility of their QOL is one, which would have been the QALE of each PMV patient had they not developed the condition. The health gap, usually considered as an indicator of health inequality, was defined and calculated as the proportion of expected loss of lifetime utility of patients with PMV in comparison with age- and gender-matched hypothetical referents simulated from vital statistics of Taiwan [33]. To facilitate the computation, we used a software program, MC-QAS, which was built on the *R* statistical package for quality adjusted survival estimation and 300-month extrapolation and can be freely downloaded from the following website: http://www.stat.sinica.edu.tw/jshwang.

3.3 Results

The medical records of 633 patients who fulfilled the definition of PMV were abstracted and linked to the National Mortality Registry of Taiwan in 2007 to obtain their survival status. Many suffered from multiple co-morbidities, including hypertension (about half), diabetes mellitus (about two-fifths), stroke, and chronic obstructive pulmonary disease (COPD), among others, as summarized in Table 3.1. More than half required mechanical ventilation because of ventilation failure resulting from the above multiple co-morbidities or from cardiopulmonary resuscitation, whereas about one-seventh needed such services because of chronic lung conditions, including COPD. The overall one-year survival rate was 33%.

We also screened 177 patients from 5 institutions and enrolled 142 patients with PMV during 2008-2009 with a response rate of 80%, of which 55 provided their EQ-5D ratings directly and 87 were assessed through either family caregivers and/or nurses only. The demographic and clinical characteristics of the above two groups of PMV subjects were summarized in Table 3.1.

The life expectancy was 1.95 years, which was depicted as the area under the survival curve of PMV patients in Figure 3.1, and the average loss of life expectancy of these patients was 8.48 years, which was the difference between the survival curve of age- and gender matched referents and that of PMV patients, or the shadowed area in Figure 3.1. After adjustment for QOL utility values directly measured on 55 patients who were able to respond, the QALE was 0.58 quality-adjusted life years (QALY), whereas QALE of patients with poor consciousness were 0.28 and 0.29 QALY for EQ-5D measured by family caregivers and nurses, respectively. Assuming that the utility value of each referent was one throughout life time, the loss of QALE for PMV patients was 9.87 QALY (upper panel of Fig.3.2), and those of 87 patients with poor cognition and inability to respond (MMSE<15) were 10.17 and 10.16 QALY for utility values measured by family caregivers and nurses, respectively. The sensitivity analysis of substituting the utility values of the U.S. with those from the U.K. did not show a significant difference in QALE between patients and their proxies, as summarized in Table 3.2. The health gap was 94% and 97% for patients with a partial cognition and poor cognition, respectively.

3.4 Discussion

This study may be the first to simultaneously estimate lifetime survival function and quality of life in PMV patients and to obtain the quality-adjusted life expectancy and the expected lifetime utility loss, which provide empirical evidence to facilitate discussion on health policy decision among patients, their families, health-care workers, and the policy makers. We found that the life expectancy of patients using PMV was 1.95 life years, which is less than the 2.65 life years estimated by Cox et al. [34] through Markov model simulation. Moreover, the QALE estimated by this study was only 0.28-0.58 QALY, which is also much less than the 1.77 QALY that these authors reported. Although investigators would usually like to compare the results from ex ante prediction with those of ex post outcome evaluation, the two studies cannot be directly compared because of major differences in the recruited subjects and measurements. Our study has a much higher proportion of patients with poor consciousness (62% vs. 30%), and our subjects are all over 21 days of PMV and on average 10 years older than theirs (mean ages 76 vs. 66 years) [34-35]. Thus, our subjects had a poorer quality of life and lower one-year survival rate (33% vs. 42%) than others [23, 34-36]. Moreover, different types of utility measurements of QOL were applied in different studies, EQ-5D versus SF-36 or QWB (Quality of Well-being index). Hence, the estimated QALE in our patients under PMV were lower than those reported from previous studies. We therefore recommend that future research on patients with normal or better consciousness be conducted to determine the QALE more accurately for such patients with different age and gender strata.

Given the limited resources in health care, it is inevitable that most countries with a national health insurance system must consider the comparative cost-effectiveness of their decisions on resource allocation, and the common unit of QALY that simultaneously considers both mortality and morbidity (or, survival and quality of life) has become more widely used. The National Institute for Health and Clinical Excellence (NICE) in the UK [37-38] is known worldwide for such practices. However, there are still controversial issues of distributive justice in bioethics concerning potential discrimination against the aged and disabled [39-40]. As Daniels proposes in the principle of distributive justice, everyone is entitled to obtain health care up to their “normal life span” if possible [39], which is adopted in the calculation of a health gap proposed in the summarization of the population health [33]. The health gap was 94% and 97% for patients with a partial cognition and poor cognition, respectively, indicating that these patients are more disadvantaged and deserve more resources based on the principle of justice. Therefore, we recommend that more efforts be implemented to improve the long-term survival and QOL for PMV patients with different underlying causes or co-morbidities to improve the efficacy of such a treatment if the cost is paid by the patients themselves or their private health insurances. If, however, the expense of PMV is paid by national health insurance, the results of this study can facilitate a more reasonable decision among all stakeholders according to the principles of equity and efficiency. For example, are we willing to spend more resources on PMV or child health, vaccinations, and preventive care, among others? Without the above data, the task of health decision is generally difficult. In Asian countries (including Taiwan), where patients and their families are not accustomed to preparing their wills early in life or signing “Do not resuscitate” documents when they are critically ill, the estimates of QALE for patients with PMV are relevant for dialogue between all stakeholders and the public. Namely, the results provide the first evidence to sound the wake-up call for the public to contemplate and openly discuss the principles of health resources distribution for the national health insurance on PMV care.

Our study has following limitations. First, the validity of the QOL measurement for critically ill patients with an impairment of cognition or even unconsciousness must be addressed. To resolve this difficulty, we conducted a survey of the patient's proxies, including both family caregivers and nurses who directly took care of them, as did other studies [27-29, 34]. The results are summarized in a separate report, which directly compares the EQ-5D values of 55 patients with those rated by their family caregivers and nurses [31]. Because EQ-5D contains only two dimensions that require subjective rating, namely, pain/discomfort and anxiety/depression, we found minor differences of the final EQ-5D values between the patient-caregiver pairs and patient-nurse pairs, -0.03±0.14, and 0.03±0.22, respectively. The results enabled us to stratify these patients according to the severity of their cognitive ability deficits and to calculate the quality-adjusted life expectancy as a sensitivity analysis, which showed that the difference between patients with good and poor consciousness is less than 0.30 QALY (Table 3.2). Although our sample size was too small for us to further stratify into more categories according to age and gender, it seemed that the difference might not be large for patients with poor consciousness. Second, we assumed a uniform utility of one for the age and gender matched reference subjects, which over-estimated the lifetime utility of the general population and also the expected lifetime utility loss of PMV patients. However, because such an assumption is uniformly applied when we calculate the health gaps for different health conditions, the bias was minimized. Third, during the lifetime extrapolation of QOL function, it was assumed that the patients remained at the same level of QOL near the end of follow-up. Such an assumption could have resulted in an overestimation because the actual QOL might gradually decline along with aging. Fourth, the accuracy of the estimation of QALE would have improved if we had obtained quality of life measurements during the follow-up of every patient in the PMV cohort. Unfortunately, we were unable to conduct this study prospectively. Thus, we simply took another consecutive, cross sectional sample of 142 PMV patients with different duration-to-dates and applied a smoothing method for the estimation of lifelong QOL function. We have demonstrated through simulation that a random sample of more than 50 subjects would be adequate for the above estimation, or, the relative bias would be less than 5% [18]. In fact, the PMV cohort to estimate survival function and the cross sectional sample of subjects under PMV for QOL measurements seemed comparable in age, gender and Glasgow Coma Scale (Table 3.1). Fifth, we used the age-, sex- matched general population as the reference group to estimate the loss of QALE and health gap for PMV patients. As patients with PMV usually cannot survive for more than one day without such a ventilation support, it is almost impossible or extremely difficult to collect another group of patients under the same condition but without mechanical ventilation. However, future studies are indicated to collect more PMV cases and stratify them by different co-morbidities and/or underlined diseases to determine if their survival and QOL are different to further improve the cost-effectiveness for such cares. Finally, because each country may have different quality of care, and hence, different survival and QOL functions, the generalization of the results from this study to other nations may be limited.

3.5 Conclusions

The life expectancy of an average 76-year-old patient under PMV was about 1.95 years in Taiwan, which amounts to 0.58 QALY (partial consciousness) and 0.28 QALY (poor consciousness) after an adjustment for quality of life measured by EQ-5D. The estimate is useful to facilitate discussions among patients, their families, and healthcare workers for clinical decision making early and throughout the course of installing mechanical ventilation. Moreover, the results can also serve as a starting point for a public dialogue on resource allocation of the NHI on critical care, aging and palliative care. Future studies should further integrate medical cost into the estimation of the cost per QALY gained together with consideration of reduction of the health gap to preserve health equality.

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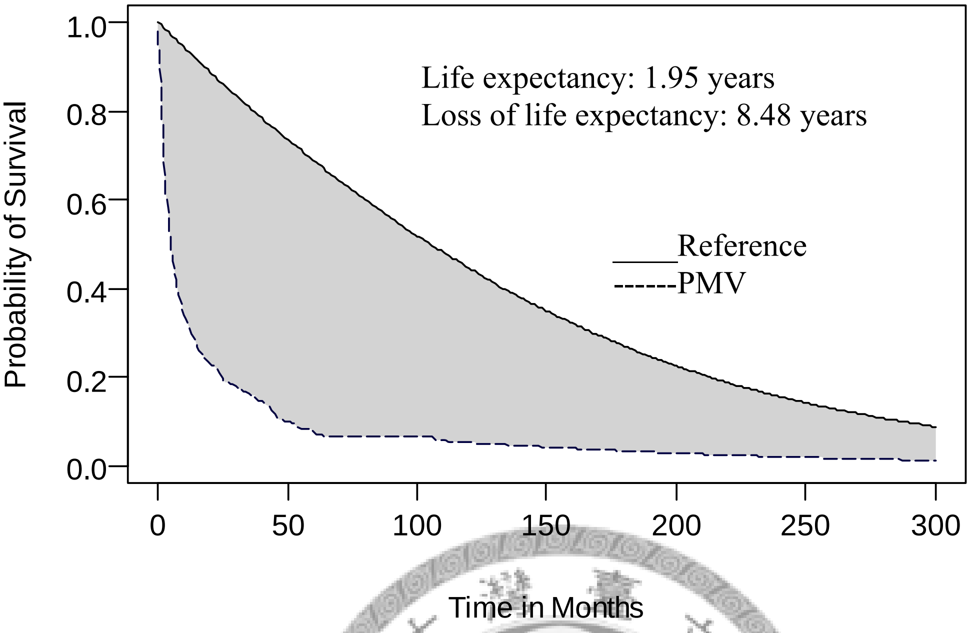

Figure 3.1 The life expectancy (namely, area under the dotted line) and loss of life expectancy (namely, shadowed area between the two curves) in years for 633 patients under PMV (prolonged mechanical ventilation) after extrapolation to 300 months.

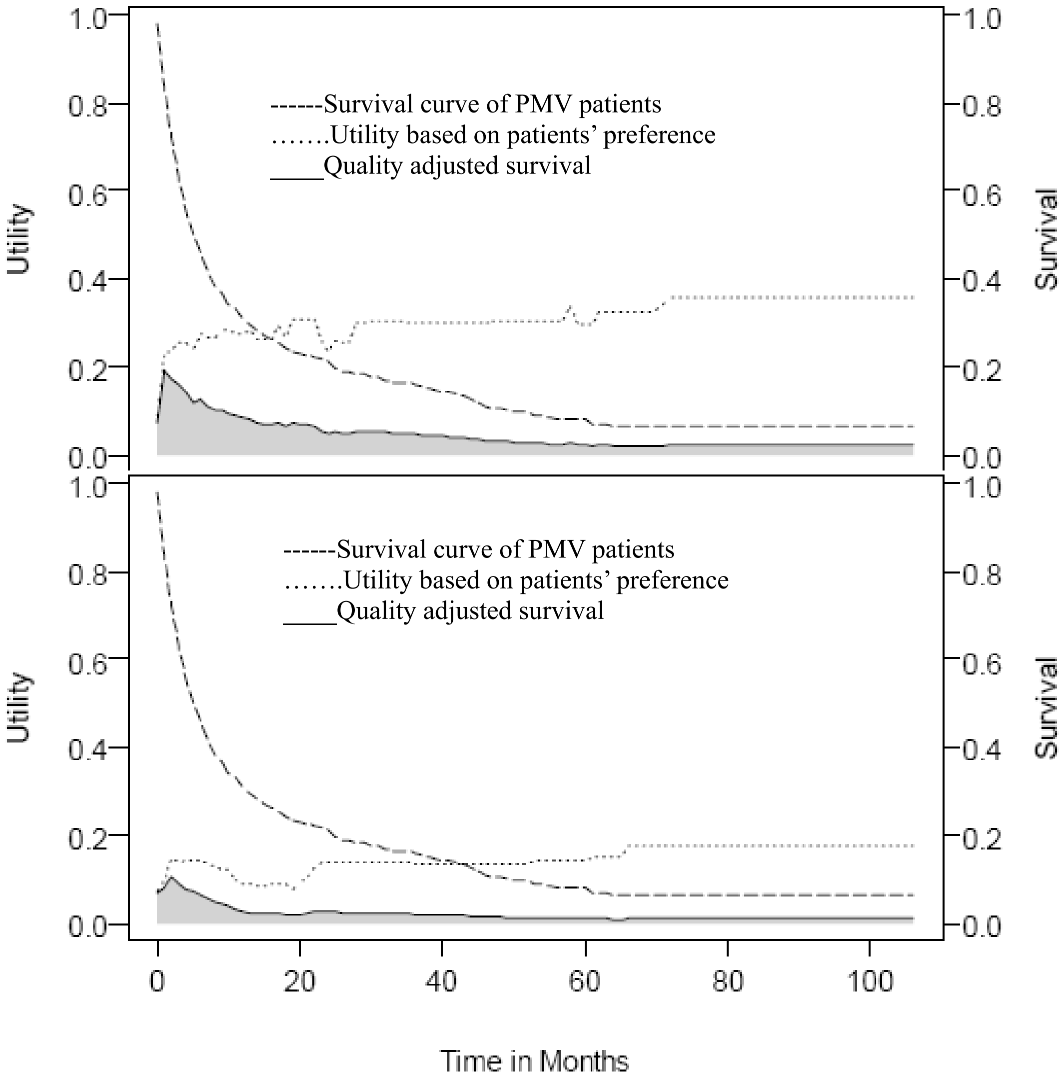

Figure 3.2 Quality adjusted survival for patients undergoing PMV (prolonged mechanical ventilation) after adjustment of survival function (N=633) with the utility values of quality of life measured with EQ-5D. The upper and lower panels depict the results of patients' preference values (N=55) and that of family caregivers' on their behalf (N=87), respectively, with the QALE (quality-adjusted life expectancy) of 0.58 and 0.28 QALY by summing the areas under the quality-adjusted survival curves.

Table 3.1 Demographic and clinical characteristics of patients under prolonged mechanical ventilation (PMV) in a cohort group to obtain the survival function and a cross-sectional sample for measurements of quality of life.

Characteristics	Cohort of PMV	Cross sectional sample of subjects under PMV
Calendar years of collection	1998-2007	2008-2009
Total number of patients	633	142
Mean age in year (S.D.)	76 (12)	75 (12)
% Female	45	43
Major underlying diseases and comorbidities		
% Hypertension	48	28
% Diabetes mellitus	40	25
% Cerebrovascular diseases	31	18
% Chronic Obstructive Pulmonary Disease	27	32
% End stage renal disease	13	11
% Asthma	7	4
% Liver cirrhosis	3	2
% Coronary artery disease	13	6
Reasons for mechanical ventilation		
% Apnea or required resuscitation	12	7
% Ventilatory failure	46	45
% Oxygenation failure	14	6
% Post-operation	10	7
% Airway protection	1	1
% Others	17	34

PMV, prolonged mechanical ventilation; SD, standard deviation.

Table 3.2 Quality-adjusted life expectancy (QALE, in years) and expected lifetime loss of utility for patients under PMV (prolonged mechanical ventilation) based on different value systems of EQ-5D and patient's cognition for sensitivity analysis

Categories Country of value system for EQ-5D	QALE (SE)		Expected lifetime loss of utility (SE)	
	U.K.	U.S.	U.K.	U.S.
Patients with partial cognition and ability to respond (Mini-Mental State Exam, MMSE≧15, n=55)				
QOL measured by patients (n=55)	0.74 (0.13)	0.58 (0.09)	9.73 (0.13)	9.87 (0.09)
QOL measured by family care-givers (n=44)	0.67 (0.15)	0.61 (0.18)	9.80 (0.16)	9.84 (0.19)
QOL measured by nurses (n=53)	0.70 (0.16)	0.64 (0.15)	9.77 (0.11)	9.81 (0.15)
Referents (age- and sex- matched)	10.47 (0.02)	10.45 (0.02)	-	-
Patients with poor cognition and inability to respond (MMSE<15, n=87)				
QOL measured by family care-givers (n=81)	0.44 (0.09)	0.28 (0.05)	9.98 (0.13)	10.17 (0.06)
QOL measured by nurses (n=81)	0.43 (0.09)	0.29 (0.05)	9.99 (0.09)	10.16 (0.05)
Referents (age- and sex- matched)	10.42 (0.02)	10.45 (0.02)	-	

MMSE, mini-mental state exam; PMV, prolonged mechanical ventilation; QALE, quality-adjusted life expectancy; QOL, quality of life; SE, standard error.

Cost-effectiveness of applying prolonged mechanical ventilation in Taiwan

(Chapter 4)

Abstract

Objective: The conventional incremental cost-effectiveness ratio (ICER) and cost-per-expected life in patients undergoing prolonged mechanical ventilation (PMV), stratified by different underlying diseases, were determined.

Design and patients: A nationwide sample of 50,481 patients who had received continual mechanical ventilation for more than 21 days was collected during 1997-2007. After stratifying the patients according to specific diagnoses, a latent class analysis (LCA) was performed to categorize PMV patients with multiple co-morbidities into several homogeneous groups.

Measurements and Main Results: The survival functions were estimated for individual groups using the Kaplan-Meier method and extrapolated to 300 months through a semi-parametric method. The survival functions were adjusted with a utility value measured by EQ-5D from a convenient sample of 142 PMV patients to estimate the quality-adjusted life expectancies (QALE). The lifetime expenditures paid by National Health Insurance (NHI) were estimated by multiplying the average spending with the survival probability for different duration-to-dates and summed up for different groups. The results showed that PMV therapy costs over 58,000 USD (U.S.dollars) per QALY for almost all patients with poor cognition. For patients with partial cognition, PMV therapy costs less than 33,000 USD per QALY for those with cancer, liver cirrhosis, intracranial or spinal cord injuries, or multiple co-morbidities who are less than 65 years of age; it costs about 52,000-63,400 USD per QALY for those with end stage renal disease, degenerative neurological diseases, or multiple co-morbidities over age 85. All costs-per-expected life were below 38,000 USD except for those with a longer life

expectancy or QALE.

Conclusions: The conventional ICER for PMV varies greatly depending on the different underlying causes and co-morbidities. The maintenance treatment for PMV patients with poor cognition may be the least cost-effective. The indicator of cost-per-expected life could be considered to improve fairness in resource allocation.

4.1 Introduction

The number of patients who require prolonged mechanical ventilation (PMV) is rapidly increasing worldwide, apparently due to an aging population with multiple co-morbidities and to the increasing availability and effectiveness of this new technology [1-3]. The fact that many patients require continued respiratory care after they have been transferred to a rehabilitation facility creates a tremendous financial burden [3-4]. The National Health Insurance (NHI) of Taiwan has implemented a system of comprehensive coverage for various healthcare services, including maintenance hemodialysis and prolonged mechanical ventilation. The NHI was first established in 1995, and has been extended to cover over 99% of the citizens of Taiwan. In 1998, the Bureau of the NHI drafted a prospective payment program, which was implemented in July 2000 [5],and encouraged integrated care for chronic, mechanically ventilated patients to help relieve crowding in intensive care units after several revisions, this program ultimately covered mechanical ventilator care in the following step-down sequence: ICUs (acute stage, <21 days, fee-for-service), respiratory care centers (a subacute stage for weaning training, up to 42 days, per diem), respiratory care wards (a chronic stage or long-term care, per diem), and homecare services (a stable stage with the care provided by family caregivers, per diem). In 2005, the total number of PMV patients who required respiratory care by the NHI of Taiwan reached 30,000 and accounted for 7.5% of the total NHI healthcare expenditures, which has become one of the major threats to the sustainability of the NHI [5-6].

Most countries with a national health insurance system have adopted economic analyses to improve overall cost-effectiveness and control costs [7-9]. The conventional incremental cost-effectiveness ratio (ICER), which quantifies how many dollars are spent per QALY (quality-adjusted life year) gained, has been widely adopted in European countries, and one of the major objectives in this study is to quantify the conventional ICER for PMV with different illnesses in Taiwan. However, ICER has been criticized as unfair to people with a short life expectancy and/or poor quality of life [10], and was forbidden to be used in the newly promulgated ACA (The Patient Protection and Affordable Care Act) [11]. By extending the Daniels' position [12] that every life is equally important and is entitled to access healthcare services up to his/her life expectancy, we propose an alternative indicator, or, lifetime cost-per-expected life, of which the denominator is replaced by the QALE (quality-adjusted life expectancy) of the PMV patients.

Based on the results of our previous study of the life expectancy and quality of life in PMV patients [13-15], we further linked the healthcare expenditures dataset with the survival function in this study to estimate the conventional ICER and the cost of treatment technology per expected life in patients undergoing PMV, stratified by the different underlying diseases. We hope that the values of both indicators can be used in the deliberation on healthcare resource allocation for PMV patients.

4.2 Subjects and Methods

Study population and datasets

The present study was approved by the Institutional Review Board of the National Taiwan University Hospital before initiation (IRB number: 200912072R). A nationwide sample of 50,481 patients who were over the age of 17 and had received continual mechanical ventilation for more than 21 days during 1998-2007 was collected. The reimbursement data file obtained from the NHI of Taiwan was transformed into a research database by the National Health Research Institutes (in Chunan, Taiwan) [16]. The identification numbers of all individuals in the reimbursement data file were encrypted to protect their privacy. These files contained detailed demographic data (including birthdates and sex) and information regarding the healthcare services provided for each patient, including all payments and dates for outpatient visits, hospitalizations, prescriptions, diagnoses, and intervention procedures. The data for each inpatient hospitalization included up to 5 diagnoses, which were coded according to the International Classification of Diseases (Ninth Revision). After stratifying the patients according to specific diagnoses, a latent class analysis (LCA) was performed to categorize PMV patients with multiple co-morbidities by different age groups into several homogeneous groups, summarized in Figure 4.1. Details of this method can be found in our previous study [15].

Survival analysis and extrapolation to 300 months

Each new patient who fulfilled the criteria for PMV was followed beginning on day 21 of PMV treatment and continuing until he/she was deceased or censored on 31 December 2007. In general, most patients did not survive for more than 1-3 years, although some patients did have a longer survival time. The lifetime survival of PMV patients (up to 300 months) was thus obtained using a linear extrapolation of a logit-transformed curve of the survival ratio between the PMV and an age-matched and gender-matched reference population generated by the Monte Carlo method from the life table of the general population of Taiwan. The detailed method and mathematical proof assuming a constant excess hazard have been described in our previous reports [15, 17-21]. To facilitate the computation of the 300-month extrapolation, we used iSQoL, which is a software program that was built based on the *R* statistical package for QALE estimation and can be downloaded for free [22].

Quality of life data

To estimate the QOL utility function for these patients, we recruited a cross sectional sample of 142 PMV subjects [13] during 2008-2009 who, after 21 days, continued to receive care from five institutions in Taiwan. Informed consent was obtained from every patient or his/her family caregiver. For subjects with basic cognition who were able to communicate their responses and to achieve a score of more than 15 on a mini-mental state examination (MMSE) [23-24], we conducted QOL measurements with the EQ-5D via direct face-to-face interviews. When patients' level of cognition was too poor for them to communicate with the interviewer, family caregivers and nurses were used as proxies [25-28]. We have summarized the detailed methods for validating measurements in another study [13]. The duration-to-date for each measurement is defined counting from the 21st day after PMV to the date of the interview by the researcher; a cross sectional sample of patients with PMV was obtained, of which the kernel-type smoothing method (moving average of the nearby 10%) was performed to calculate the mean QOL throughout the follow-up time period of 9 years [20, 21]. The QOL value after 9 years was assumed to be the same as the end of follow-up.

Quality-adjusted life expectancies (QALE)

The lifetime survival probabilities along the duration-to-dates (or time after beginning PMV) were multiplied (or adjusted) with the QOL values measured from EQ-5D to obtain a quality-adjusted survival curve, of which the sum of the total area under this curve was the QALE with QALY as the common unit [21]. Due to uncertainties in the estimation of QALE after installation of PMV, we conducted a sensitivity analysis based on a patient’s level of cognition to see whether different cognition levels had a significant effect on the incremental cost-effectiveness ratio.

Lifetime healthcare expenditures paid by the NHI

We calculated the lifetime healthcare expenditures (or, cost reimbursed by the NHI) of 50,481 PMV patients from the 21st day of PMV treatment to the end of life, including patients in inpatient and outpatient care. The calculation process was as follows. First, for each specific diagnosis group, we summed up the average claimed expenditure for each month and divided that cost by the corresponding number of PMV patients who were still alive during that month to obtain the average monthly cost. The costs of different years were adjusted to the Consumer Price Indices (CPI) of 2010. Second, this value was then multiplied by the monthly survival probability for each specific diagnosis group throughout its lifetime and then was summed to obtain the lifetime cost. We further categorized the healthcare expenditures into those directly related to PMV treatment according to the IDS (integrated delivery services) [5].

Conventional incremental cost-effectiveness ratio (ICER) and cost-per-expected life

The ICER of PMV treatment for each group was calculated by the following formula:

Incremental cost per QALY gained= (Estimated total lifetime cost with PMV treatment per patient - Estimated total lifetime cost without PMV treatment per patient)/ (Estimated QALE with PMV treatment per patient- Estimated QALE without PMV treatment per patient) = $\triangle$cost/$\triangle$QALY. Because patients under PMV treatment usually cannot survive for more than 1 day, we assumed that the cost and QALE without such a treatment was zero.

By taking the position that every citizen is entitled to access healthcare services up to his/her life expectancy, we replaced the denominator of the conventional ICER,

△QALY, with the proportion gained for life expectancy under the treatment technology, which is the △QALY gained divided by the QALE after the PMV treatment. The modified cost-effectiveness ratio is renamed as "lifetime cost-per-expected life" and was calculated by the following formula: △lifetime cost/ (△QALY gained/QALE after treatment). Since the patient's life is totally sustained by the PMV, the △lifetime cost is the same as the cost of treatment; the △QALY gained is the same as the QALE after treatment, and the denominator of the new indicator becomes one. Hence, the new indicator itself is the △lifetime cost or △cost of treatment.

4.3 Results

A total of 50,481 new patients receiving PMV were included during the study period, with an average lifetime cost of 27,902 USD. The QALE for patients with partial cognition was 0.98 QALY (Figure 4.2) the mean age was 72±14.5 years, and 32% of them were from the Southern part of Taiwan. The claimed cost ranged from 46,710 USD to 99,650 per QALY, and 27,902 USD per expected life.

QALE of PMV patients with specific underlying diseases

The QALE of PMV patients with different specific underlying diseases are summarized in Table 4.1, which indicates that the QALE of PMV patients that had partial cognition was usually two times greater than that of those with poor cognition. The QALE of those with injuries or liver cirrhosis was generally better than those with chronic renal failure or cancer. When a patient contracted both cancer and chronic renal failure, the QALE was the lowest, with 0.16 and 0.36 QALY for patients with poor and partial cognition, respectively.

QALE of PMV patients with multiple co-morbidities

Of the 23,697 PMV patients with multiple co-morbidities, the latent class model usually yielded 3-4 clusters, including heart diseases, septicemia/shock, chronic obstructive pulmonary diseases and/or others (e.g., urinary tract infections), after stratifying by age, as summarized in Table 4.2. The QALE of PMV patients with COPD was generally better than those of other clustered groups, especially those with septicemia/shock.

Lifetime healthcare expenditure of PMV patients

The curves of monthly healthcare expenditure multiplied by the corresponding survival probability for each time *t* period are depicted in Figure 4.3. We only illustrated such calculations for subjects with cancer, injuries, and patients younger than 64 years old with chronic obstructive pulmonary disease (COPD) as examples. The total summed area under the curve is the estimated lifetime cost paid by the NHI for the specific illness. Among them, lifetime cost of care for PMV patients with cancer was the lowest of all specific underlying diseases, as summarized in Table 4.1, and that of septicemia/shock was the lowest among patients with multiple co-morbidities after stratification by ages (Table 4.2). In general, the expenditures directly spent for the PMV technology occupied over more than two-thirds of the total, although different health conditions might still vary.

Incremental cost per QALY versus lifetime cost (per expected life)

The results show that PMV therapy costs over 58,000 USD per QALY for all patients with poor cognition, except for those with liver cirrhosis, intracranial or spinal injuries, or septicemia/shock who are less than 65 years of age. For patients with partial cognition, PMV therapy usually costs less than 33,000 USD per QALY for those with cancer, liver cirrhosis, intracranial or spinal cord injuries, or multiple co-morbidities and less than 65 years of age; it costs about 34,000-45,000 USD per QALY for patients with stroke or multiple co-morbidities and less than 84 years of age; and about

52,000-63,400 USD per QALY for those with end stage renal disease, degenerative neurological diseases, or multiple co-morbidities who are over age 85. In general, the lifetime costs of PMV patients would be larger, if the patients could survive longer. All lifetime costs (per expected life) for PMV were below 38,000 USD except for patients with a longer survival for more than 3-4 years, including degenerative neurological diseases or multiple co-morbidities at an age of less than 65, as summarized in Table 4.1 and Table 4.2. Figure 4.4 depicts the association of cost-per-QALY and lifetime cost for PMV patients with partial cognition under different categories.

4.4 Discussion

To our knowledge, this study is the first to analyze a national PMV dataset to estimate the ICER stratified by age and different clusters of diagnoses. Because we extended the interpretation of Professor Daniels' position that every citizen is entitled to access healthcare services up to his/her life expectancy, we were able to provide the estimates of one more indicator related to cost-effectiveness, or, lifetime cost per expected life. Because all co-payments were waived for PMV patients in Taiwan and the healthcare expenditures paid by the NHI in different years were fully adjusted to the monetary value of the year 2010, the estimation of lifetime expenditures for the NHI would be relatively accurate. The sensitivity analysis with different annual discount rates, for example, 5%, generally does not affect the lifetime expenditures and health policy decisions because these patients usually survive for less than 2-3 years. To control the potential confounding by different underlying diseases and levels of cognition, we have stratified all patients into those with specific illnesses (Table 4.1) and those with multiple co-morbidities and age ranges (Table 4.2), according to two distinct cognition levels. Thus, we tentatively conclude that our estimation is the best available and could be useful to all of the stakeholders in deliberations about resource allocation in Taiwan.

The gross domestic product (GDP) per capita in 2010 was 18,588 USD in Taiwan [29]. If we adopt the criteria suggested by WHO-CHOICE (CHOosing Interventions that are Cost Effective) of using 1-3 times the GDP as the threshold for cost-effectiveness [30] , then providing PMV to all patients with poor cognition would not be cost-effective except for those with liver cirrhosis, intracranial or spinal injuries, or septicemia/shock and less than 65 years of age. For patients who were able to communicate or were partially cognitive, we found that those who suffered from end stage renal disease or degenerative neurological diseases, or from multiple co-morbidities who were over 85 years of age also cost more than 3 times the GDP per QALY, while PMV therapy usually cost less than 33,000 USD (or, less than 1.4 GDP) per QALY for those with cancer, liver cirrhosis, intracranial or spinal cord injuries, or with multiple co-morbidities and less than 65 years of age.

Alternatively, if we consider that every life is entitled to the lifesaving treatment, such as the PMV, up to one's life expectancy, then we should look at the results of cost-per-expected life in Tables 4.1 and 4.2. Since the denominator is replaced by an expected life that is equal for everyone, the indicator seems to correspond better to a fair distribution for health needs of PMV for different conditions. All costs per expected life were below 38,000 USD except for patients with degenerative neurological diseases or with multiple co-morbidities at an age of less than 65. In other words, most of these PMV patients would spend less than 2 times of GDP for one life. Figure 4.4 depicts the association of cost-per-QALY and cost-per-expected life for PMV patients with partial cognition under different categories. From medical point of view, one would be willing to invest more resources that are effective in saving the patient or able to wean the patients from ventilator. Simultaneously, one would also try to avoid spending too much money on illnesses with short life expectancies or poor prognosis. Hence, the NHI might set up a ceiling value for cost-per-expected life under the budget constraint. It appears that a trade-off between cost-effectiveness and fairness in distribution would be unavoidable. Therefore, we recommend that such a decision be made during the deliberation process and involve all stakeholders [31]. Moreover, values of both indicators must be quantified for health conditions other than those requiring PMV to give a more extended comparison. For example, are we willing to spend more resources on PMV or child health, vaccinations, and preventive care, among others services? This decision will require difficult balancing of what is good for patients and their families, incentives for providers of healthcare services, sustainability of the NHI, and what is good for society. Our results could serve as sounding the wake-up call for the public to contemplate and openly discuss the principles of health resources distribution for national health insurance, including PMV care.

Our study has some limitations. First, because there are no MMSE data in the NHI database, we were unable to directly quantify the QALE for each individual condition. The estimation in this study is, in fact, a sensitivity analysis based on the assumption that there are two largely different health states defined by cognitive conditions. Because the utility value for patients with poor consciousness is generally low [13, 32] and the usual life expectancy is less than 2-3 years [15, 33], the potential bias of estimation would usually be minimal, should it happen. Second, during the lifetime extrapolation of the QOL function, it was assumed that the patients continued to stay at the same level of QOL as measured near the end of follow-up. Such an assumption could result in an overestimation of the QALE, because the actual QOL might gradually decline with aging and increased co-morbidities [34-35]. But because the QOL of PMV patients was very poor even when they had partial cognition, our estimates may only be a slight overestimation and probably would not alter a policy decision.

4.5 Conclusions

The conventional ICER for PMV varies greatly depending on different underlying causes and co-morbidities. Among these patients, maintenance treatments for PMV patients with poor cognition or patients more than 85 years of age might be the least cost-effective. Because the proposed indicator of cost-per-expected life seems to be more equitable for those with health conditions and a short life expectancy and/or poor quality of life than the conventional ICER, we recommend that it be also considered in future deliberations about healthcare resources allocation.

4.6 References

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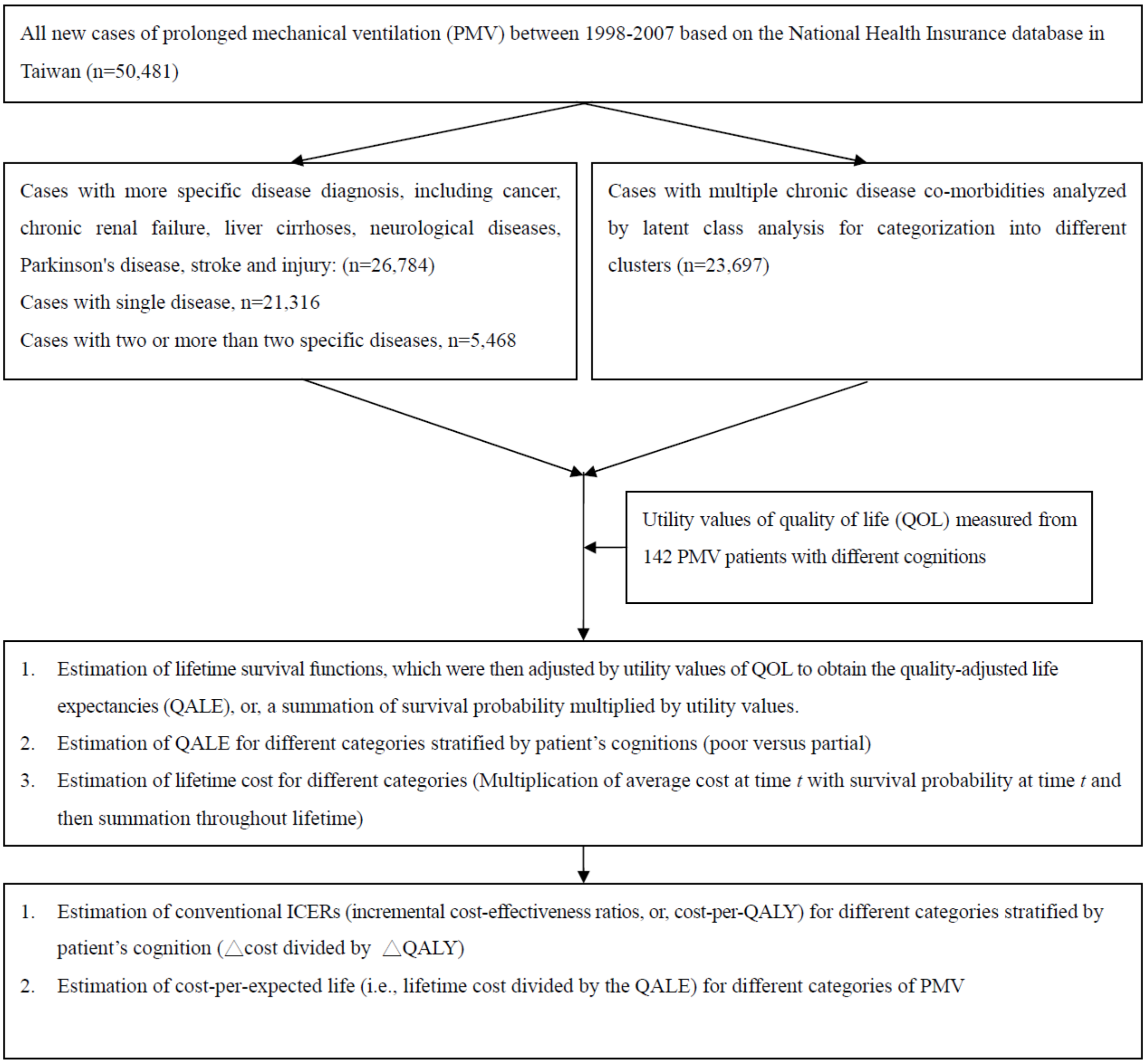

All new cases of prolonged mechanical ventilation (PMV) between 1998-2007 based on the National Health Insurance database in Taiwan (n=50,481)

Cases with more specific disease diagnosis, including cancer, chronic renal failure, liver cirrhoses, neurological diseases, Parkinson's disease, stroke and injury: (n=26,784)

Cases with single disease, n=21,316

Cases with two or more than two specific diseases, n=5,468

Cases with multiple chronic disease co-morbidities analyzed by latent class analysis for categorization into different clusters (n=23,697)

Utility values of quality of life (QOL) measured from 142 PMV patients with different cognitions

1. Estimation of lifetime survival functions, which were then adjusted by utility values of QOL to obtain the quality-adjusted life expectancies (QALE), or, a summation of survival probability multiplied by utility values.
2. Estimation of QALE for different categories stratified by patient's cognitions (poor versus partial)
3. Estimation of lifetime cost for different categories (Multiplication of average cost at time *t* with survival probability at time *t* and then summation throughout lifetime)

1. Estimation of conventional ICERs (incremental cost-effectiveness ratios, or, cost-per-QALY) for different categories stratified by patient's cognition (△cost divided by △QALY)
2. Estimation of cost-per-expected life (i.e., lifetime cost divided by the QALE) for different categories of PMV

Figure 4.1 Flow chart of the computation process for cost-per-QALY (quality-adjusted life year) and cost-per-expected life

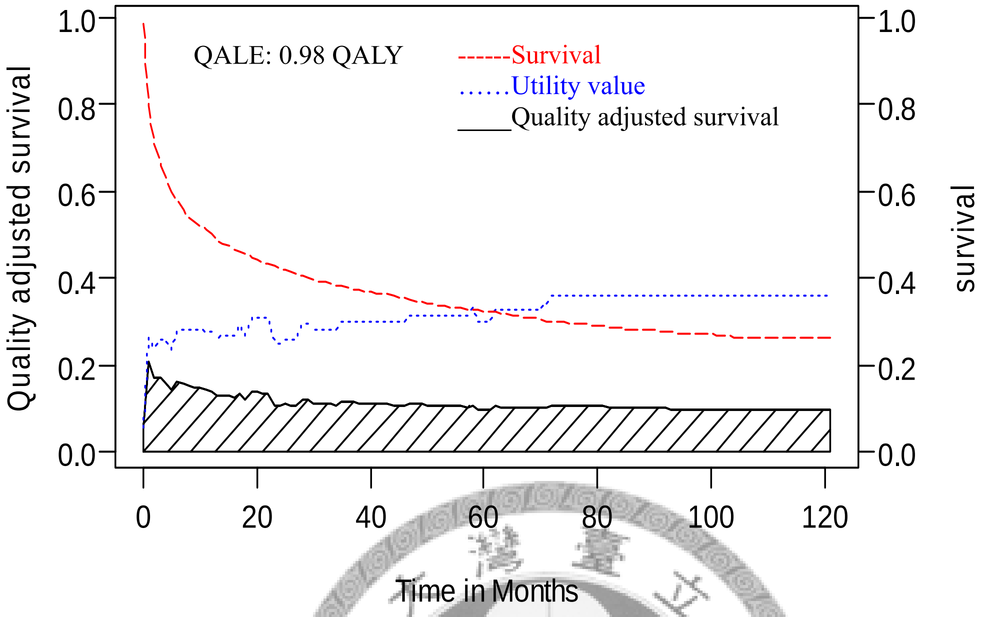

Figure 4.2 Quality adjusted survival for patients undergoing PMV (prolonged mechanical ventilation) with partial cognition after adjustment for survival function (N=50,481) with the utility values of quality of life measured with EQ-5D (N=55). The result of QALE (quality-adjusted life expectancy) of an average patient was 0.98 QALY by summing the areas under the quality-adjusted survival curve.

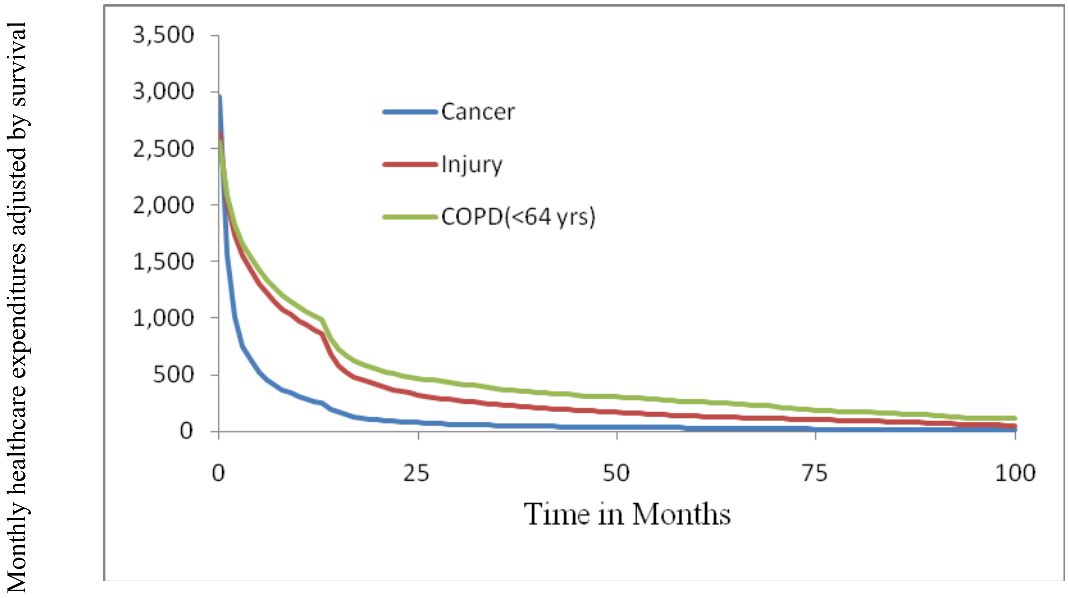

Figure 4.3 Curves of average monthly healthcare expenditures adjusted by survival probability plotted along time after beginning PMV (prolonged mechanical ventilation), stratified by cancer, injuries, and COPD (chronic obstructive pulmonary disease) cases with age less than 64 years old. The areas under these curves were the lifetime costs paid by the National Health Insurance.

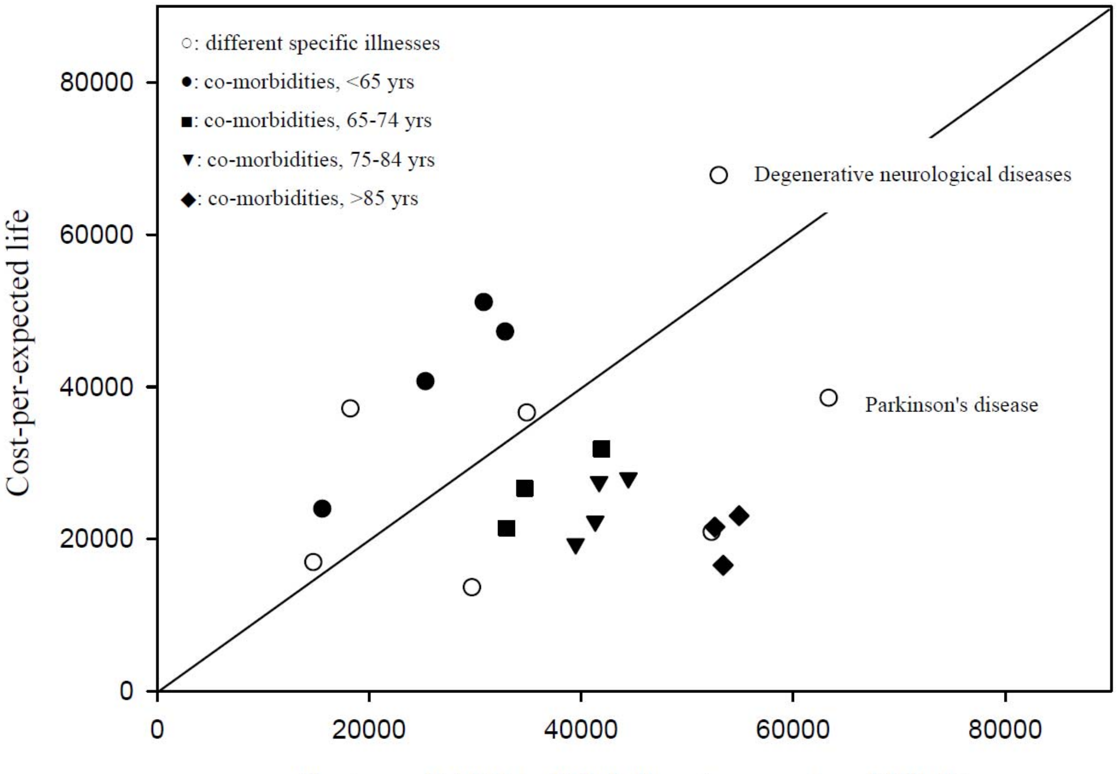

Figure 4.4 Plot of association between the conventional ICER (or, incremental cost-per- QALY [quality-adjusted life year] gained) and the cost-per-expected life for PMV patients with different specific illnesses [○] and multiple co-morbidities stratified by age groups (<65[●], 65-74[■], 75-84[▼], and >84[◆] years old)

Table 4.1 Cost-per-QALY (quality-adjusted life year) and cost-per-expected life for patients undergoing prolonged mechanical ventilation in Taiwan, stratified by different underlying diseases, with sensitivity analysis of quality-adjusted life expectancy (QALE) under different states of cognition.

	Number of cases	Mean age at diagnosis (Years) (SD) [a]	Lifetime cost ($US) for treatment		QALE(QALY)(SE) [b]		Cost-per-QALY		Cost-per-expected life
			Total	PMV related	partial cognition	poor cognition	partial cognition	poor cognition	
Cases with single specific disease (overall)	21,316	69 (15)	28,350	20,950	0.93 (0.17)	0.47(0.09)	30,484	60,319	28,350
Cancer	5,367	70 (14)	13,656	9,802	0.46 (0.08)	0.20 (0.03)	29,687	68,280	13,656
Chronic renal failure	2,032	73 (12)	20,916	14,102	0.40 (0.09)	0.18 (0.04)	52,290	116,200	20,916
Liver cirrhosis	1,478	65 (17)	16,948	13,545	1.15 (0.22)	0.50 (0.13)	14,737	33,896	16,948
Multiple sclerosis or degenerative nervous system conditions	378	65 (17)	67,804	61,009	1.28 (0.25)	0.56 (0.14)	52,972	121,079	67,804
Parkinson's disease	341	79 (7)	38,556	33,763	0.59 (0.14)	0.26 (0.07)	63,349	148,292	38,556
Stroke	6,765	70 (13)	36,611	29,226	1.05 (0.20)	0.46 (0.09)	34,868	79,589	36,611
<64 yrs	1,955	-	47,161	31,487	1.60 (0.39)	0.72 (0.13)	29,476	65,501	47,161
65-74 yrs	1,818	-	37,385	31,595	1.14 (0.16)	0.40 (0.09)	32,794	93,463	37,385
75-84 yrs	2,176	-	34,582	29,666	0.61 (0.08)	0.27 (0.04)	56,692	128,081	34,582
>85 yrs	816	-	25,920	23,235	0.49 (0.06)	0.21 (0.03)	52,898	123,429	25,920
Intracranial and/or spinal cord injury or poisoning	4,955	65 (19)	37,161	25,019	2.04 (0.39)	0.89 (0.18)	18,216	41,754	37,161
<64 yrs	1,949	-	49,046	28,034	3.40 (0.68)	1.47 (0.31)	14,425	33,365	49,046
65-74 yrs	1,116	-	33,002	23,836	1.18 (0.18)	0.51 (0.09)	27,968	64,710	33,002
75-84 yrs	1,366	-	28,808	26,173	0.82 (0.12)	0.33 (0.07)	35,132	87,297	28,808
>85 yrs	524	-	26,056	23,350	0.52 (0.09)	0.22 (0.03)	50,108	118,436	26,056
Cases with more than	4,772	45 (14)	27,715	20,677	0.93 (0.17)	0.40 (0.07)	29,801	69,288	27,715

two specific diseases									
Cancer and Chronic renal failure	165	71 (11)	20,039	14,331	0.36 (0.15)	0.16 (0.06)	55,664	125,244	20,039
Cancer and others	1,609	70 (14)	17,053	15,589	0.58 (0.13)	0.26 (0.04)	29,402	65,588	17,053
Chronic renal failure and others	743	70 (13)	23,024	14,333	0.52 (0.14)	0.23 (0.07)	44,277	100,104	23,024

a: SD, standard deviation; b: SE, standard error of the mean

Table 4.2 Cost-per-QALY (quality-adjusted life year) and cost-per-expected life for patients undergoing prolonged mechanical ventilation in Taiwan, stratified by different co-morbidities and categorized by latent class analysis stratified by age, with sensitivity analysis of quality-adjusted life expectancy (QALE) under different states of cognition.

	Number of cases	Lifetime cost ($US) for treatment		QALE (QALY) (SE)[a]		Cost-per-QALY		Cost-per-expected life
		Total	PMV related	partial cognition	poor cognition	partial cognition	poor cognition	
<65 yrs								
Heart diseases	616	40,732	28,248	1.61 (0.41)	0.70 (0.19)	25,299	58,189	40,732
Septicemia/ Shock	919	23,972	18,358	1.22 (0.23)	0.64 (0.14)	19,649	37,456	23,972
Urinary tract infections/ Shock	197	47,260	28,733	1.43 (0.35)	0.62 (0.18)	33,049	76,226	47,260
COPD[b]	1,788	51,127	40,314	1.66 (0.24)	0.72 (0.14)	30,799	71,010	51,127
65-74 yrs								
Heart diseases	1,074	26,690	22,028	0.77 (0.14)	0.34 (0.07)	34,662	78,500	26,690
Septicemia/ Shock	1,824	21,427	18,573	0.65 (0.09)	0.28 (0.04)	32,965	76,525	21,427
COPD[b]	2,499	31,849	27,132	0.76 (0.11)	0.33 (0.06)	41,907	96,512	31,849
75-84 yrs								
Heart diseases	1,404	22,320	18,283	0.54 (0.11)	0.24 (0.05)	41,333	93,000	22,320
Septicemia/ Shock	2,856	19,341	17,895	0.49 (0.03)	0.22 (0.05)	39,471	87,914	19,341
COPD[b]	4,142	28,004	25,538	0.63	0.28	44,451	100,014	28,004

				(0.09)	(0.05)			
Respiratory diseases	1,345	27,517	26,046	0.66 (0.13)	0.29 (0.05)	41,692	94,886	27,517
>85 yrs								
Heart diseases	870	21,573	19,467	0.41 (0.05)	0.18 (0.03)	52,617	119,850	21,573
Septicemia/ Shock	1,359	16,553	14,805	0.31 (0.05)	0.14 (0.02)	53,397	118,236	16,553
COPD[b]	2,804	23,057	21,649	0.42 (0.06)	0.19 (0.03)	54,898	121,353	23,057

a: SE, standard error of the mean; b: COPD, chronic obstructive pulmonary disease

Conclusion

(Chapter 5)

The number of new patients undergoing treatment of PMV has increased rapidly during the last decade in Taiwan. The life expectancies of PMV patients suffering from degenerative neurological diseases, stroke, or injuries tended to be longer than those with chronic renal failure or cancer. Patients with chronic obstructive pulmonary disease survived longer than did those co-morbid with other underlying diseases, especially septicaemia/shock. QOL assessments from family caregivers agreed more closely with patients than did those from nurses using EQ-5D evaluations for patients with partial cognition, but either proxy was acceptable for rating PMV patients with poor cognition. The life expectancy of an average 76-year-old patient under PMV was about 1.95 years in Taiwan, which amounts to 0.58 QALY (partial cognition) and 0.28 QALY (poor cognition) after an adjustment for quality of life measured by EQ-5D. The ICER for PMV varies greatly depending on different underlying causes and co-morbidities. Among these patients, maintenance treatments for PMV patients with poor cognition or patients more than 85 years of age might be the least cost-effective. Theses results of poor prognosis would provide stakeholders evidence for communication to facilitate clinical decisions, and also to gradually develop the clinical guidelines for PMV in our society. Moreover, the results can also serve as a starting point for a public dialogue on resource allocation of the NHI on critical care, aging and palliative care. For patients with poor consciousness, we recommend holistic care to prevent from prolonged dying process. We also should promote the life education to sign DNR (Do not resuscitate) in health or early stage of disease.

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Measurement of quality of life using EQ-5D in patients on prolonged mechanical ventilation: comparison of patients, family caregivers, and nurses

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Abstract
Purpose This study reports how QOL (quality of life) assessments differ between patients on prolonged mechanical ventilation (PMV) and their proxies (family caregivers and nurses).
Methods We enrolled consecutive subjects on PMV for more than 21 days from five institutions. We conducted QOL assessments using the Taiwanese version of the EQ-5D in face-to-face interviews. Direct caregivers (family members and nurses) also completed the EQ-5D from the patient's point of view.
Results For 55 of the 142 enrolled patients who were able to assess their QOL, we recruited 44 patient–family caregiver pairs, 53 patient–nurse pairs, and 42 family caregiver–nurse pairs. There were 81 family caregiver–nurse pairs out of 87 patients with poor cognition. The agreement between patient–family caregiver pairs was generally higher than that of patient–nurse pairs. As the proportions of exact agreement between family caregivers and nurses for patients with poor cognition were 98–99% for observable dimensions of mobility, self-care, and usual activities, they lead to a minimal difference in the final values.
Conclusions QOL assessments from family caregivers agreed more closely with patients than did those from nurses using EQ-5D evaluations for patients with clear cognition, but either proxy was acceptable for rating PMV patients with poor cognition.

Keywords Prolonged mechanical ventilation · Proxy · Quality of life · EQ-5D · Utility

Abbreviations

PMV	Prolonged mechanical ventilation
QO	Quality of life
ICU	Intensive care unit
RCC	Respiratory care center
RCW	Respiratory care ward
IRB	Institutional review board
MMSE	Mini-mental status examination
EQ-5D	EuroQol five-dimensional
ICC	Intra-class correlation coefficient

Introduction

Patients who require prolonged mechanical ventilation (PMV) are rapidly increasing in number, as the improved

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quality of care in ICUs (intensive care units) has resulted in long-term survival for many patients [1, 2]. However, these patients often require continued respiratory care after transfer to a rehabilitation facility, skilled nursing facility, or home care, creating financial burdens for the insurance system and/or the patients' families [1, 3]. Several studies have reported [1, 4–6], however, that survivors often feel their quality of life (QOL) to be acceptable.

The National Health Insurance (NHI) of Taiwan uses a system of comprehensive coverage for various health care services, including maintenance hemodialysis and chronic respiratory care. The NHI was first established in 1995 and has been extended to cover over 99% of Taiwanese citizens [7, 8]. In 1998, the Bureau of NHI drafted a prospective payment program to encourage integrated care for mechanically ventilated patients, which was implemented in July 2000 [9]. After several revisions, this program ultimately covered four types of mechanical ventilator care: ICU care (acute stage, <21 days), respiratory care center (RCC, a sub-acute stage for weaning training of up to 42 days), respiratory care ward (RCW, a chronic stage or long-term care), and home care service (stable stage, in which the patient is cared for directly by family caregivers).

Unlike patients on PMV in other countries [10–14], many patients in Taiwan suffer from concomitant cognitive impairments that preclude direct assessment of their subjective QOL, making evaluation by proxy unavoidable in many cases. The objective of this study was to evaluate the utility assessment of QOL in patients on PMV and to compare patients' own QOL assessments with those made on their behalf by proxies (family caregivers and professional nurses).

Methods

Subjects and methods

We recruited subjects from five institutions in northern and southern Taiwan and consecutively enrolled current PMV subjects who had already been on mechanical ventilation for at least for 21 days at various levels of care (ICU, RCC, and RCW): 1 medical center, 1 regional hospital, and 3 small local hospitals were included. The study began after approval was obtained from the Institutional Review Boards (IRBs) of the National Taiwan University Hospital and the Chia-Yi Christian Hospital. The three local hospitals also approved the study after reviewing the approval documents of the two major IRBs above. For subjects with basic cognition who were able to communicate (including through clear body language) and who scored at least 15 on the mini-mental status examination (MMSE) [15], we conducted QOL measurements using the EQ-5D in direct, face-to-face interviews. The primary caregivers (family members and nurses) were also asked to independently complete the EQ-5D questionnaire from the patient's point of view, i.e., each proxy rated how he or she thought the patient would rate his or her own QOL on the day of the interview. All the interviews with the patient and his/her proxy were required to be finished within 3 days, and we also made sure that the individual patient's clinical condition was stable by verifying with the medical records. The proxy's results were directly compared with the patient's own rating, which was considered to be the gold standard.

Quality of life measured by EQ-5D

The utility value of the QOL for patients on PMV was estimated using the EuroQol five-dimensional (EQ-5D) questionnaire, a generic preference-based instrument. The five dimensions assessed by the EQ-5D are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, with three levels of severity (no problems, some/moderate problems, and severe/extreme problems). This provides a utility value that ranges from 0 to 1 based upon the five-dimensional health state classification, in which 0 represents the worst health status and 1 represents perfect health [16, 17]. The EQ-5D instrument is a valid and reliable tool for measuring health status that has been extensively used in many countries as an outcome measure, including for critically ill patients [18–20]. It was also recently applied in Taiwan with good validity and moderate reliability [21]. We applied the value systems of the United States and the United Kingdom as a comparison [17, 22]. There is general agreement that patients are the best raters of their QOL; however, when a patient's mental status is too poor, family caregivers and nurses may be considered as proxies [11–13]. QOL assessment by EQ-5D was conducted by three research assistants who were first trained in the standard operating procedure. For each patient and his/her proxy, the researcher recorded characteristics including age, gender, education, marital status, relationship to the patient, whether or not the proxy lived with the patient, frequency of caring for the patient, location (ICU or RCC or RCW), Glasgow Coma Scale (GCS), presence/absence of tracheotomy and duration of mechanical ventilation, and history of depression. The duration-to-date for each measurement was defined as beginning on the first day after PMV and ending on the date of interview by our researcher.

Statistical analysis

Binary and categorical variables were summarized using frequency counts and percentages. Continuous variables are presented as means if normally distributed. The agreement between QOL scores from patients, family caregivers, and nurses for each dimension was determined for each pair by calculating weighted kappa scores [23]. To evaluate any systematic tendency for proxy respondents to overestimate or underestimate QOL, we computed the patient–proxy and proxy–proxy mean differences in the final utility value of the EQ-5D. The mean difference between pair-scores and values were tested with the rank sum and paired *t*-tests to detect any significant difference when the sample size is small. We calculated the effect size by dividing the mean patient–proxy difference by the standard deviation of the patient responses. The magnitude of the standardized difference can be interpreted as follows: $|d| = 0.2$, a small difference; $|d| = 0.5$, a moderate difference; and $|d| = 0.8$, a large difference [24]. The agreement between patients and proxies of the summary index of EQ-5D was assessed with one-way intra-class correlation coefficients (ICC) [25, 26]. An ICC or weighted kappa less than 0.4 was considered to indicate poor agreement, 0.40–0.75 indicated moderate to good agreement, and values >0.75 indicated excellent agreement [23, 27–29]. Because the group was homogeneous in disease status and marginal distribution, the statistical ICC and weighted kappa underrate agreement [30]. Thus, we calculated the proportion of exact agreement, defined as the number of same response categories chosen between the index subject and the proxy divided by the total number of rating pairs [31].

Results

Basic characteristics of respondents

A total of 177 patients were invited for this study; 142 patients accepted interviews producing a response rate of 80%, as summarized in Fig. 1. For the 55 patients able to assess their own QOL, we collected 44 patient–family caregiver pairs, 53 patient–nurse pairs, and 42 family caregiver–nurse pairs. We successfully collected 81 family caregiver–nurse pairs for 87 patients who were unable to assess their own QOL. We were unable to recruit any proxy for six patients with poor cognition.

The first proxy group (family caregivers) consisted of 129 persons; 57% were the patients' children, 58% lived with the patients, and 67% contacted the patients everyday. The second proxy group (nurses) consisted of 135 persons, 27% of whom were directly responsible for the patients' everyday care (Table 1).

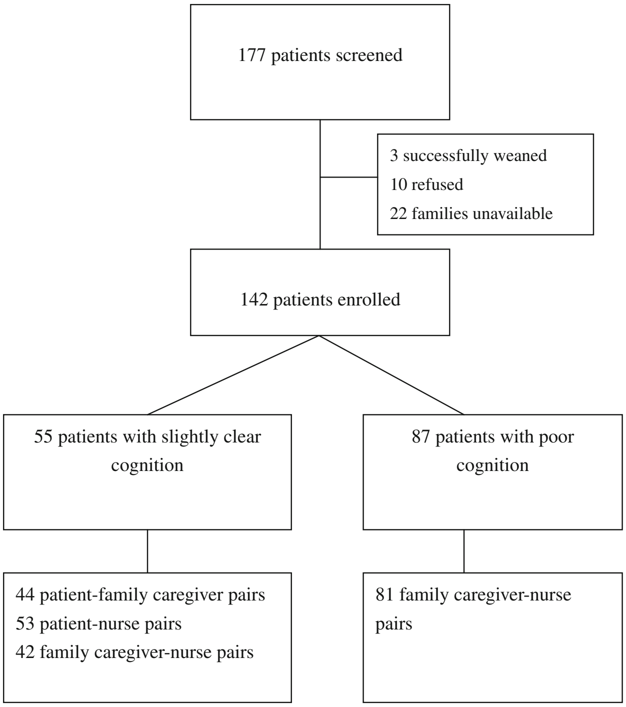

Fig. 1 Recruitment process for study participants

Table 1 Characteristics of study subjects and proxies (family caregivers and nurses)

Characteristics	Patients	Family caregivers	Nurses
Total number of subjects	55	129	135
Mean age in years (SD)	70.9 (13.2)	51.5 (11.7)	27.7 (3.6)
% Females	49	46	95
% Above junior high school education	31	56	98
% Married	96	–	–
Relationship with the patient			
% Spouse	–	26	–
% Child	–	57	–
% Others	–	17	–
% Living together	–	58	–
% Frequency of contact with patient			
Daily	–	67	27
>Once a week	–	25	54
<Once a week	–	8	19
Glasgow Coma Scale (SD)	9.9 (2.5)	–	–
% Tracheotomy	71	–	–
Duration of mechanical ventilation (months)	19.1 (26.0)	–	–

Values are expressed as means (standard deviations) or percentages

Agreement in each dimension

Although the weighted kappa scores indicated poor to moderate agreement (0.21–0.58) in the observable dimensions (mobility, self-care, and usual activities) and poor agreement (0.00–0.35) in the subjective dimensions (pain/discomfort and anxiety/depression), the proportions

Table 2 Frequency distribution of agreement among patients with fair to good cognition (mini-mental status examination score >15) for each dimension of the EQ-5D

Dimension	Patient $n = 55$ (%)	Family caregiver $n = 44$ (%)	Nurse $n = 53$ (%)	Patient–family caregiver $n = 44$ weighted kappa (confidence intervals) and [proportion of exact agreement]	Patient–nurse $n = 53$ weighted kappa (confidence intervals) and [proportion of exact agreement]
Mobility					
No problems	0	0	2 (4)		
Problems	11 (20)	8 (18)	10 (19)	0.58 (0.28–0.88)	0.28 (0.01–0.55)
Confined to bed	44 (80)	36 (82)	41 (77)	[86%]	[75%]
Self-care					
No problems	0	0	0		
Some problems	8 (15)	3 (7)	11 (21)	0.56 (0.19–0.93)	0.21 (−0.11–0.52)
Unable to wash/dress	47 (85)	41 (93)	42 (79)	[91%]	[77%]
Usual activities					
No problems	0	0	1 (2)		
Some problems	11 (20)	7 (16)	11 (21)	0.44 (0.09–0.79)	0.26 (−0.03–0.56)
Unable to perform	44 (80)	37 (84)	41 (77)	[91%]	[75%]
Pain/discomfort					
None	20 (36)	10 (23)	8 (15)		
Moderate	17 (31)	19 (43)	38 (72)	0.35 (0.13–0.57)	0.00 (−0.17–0.16)
Extreme	18 (33)	15 (34)	7 (13)	[52%]	[28%]
Anxiety/depression					
None	27 (50)	13 (30)	7 (13)		
Moderate	14 (25)	13 (30)	36 (68)	0.35 (0.13–0.57)	0.18 (0.01–0.34)
Extreme	14 (25)	18 (40)	10 (19)	[52%]	[38%]

of exact agreement were more than 75 and 28% for observable and subjective dimensions, respectively, indicating high agreement on the former dimension for both family caregivers and nurses (Table 2). Family caregivers in particular displayed better agreement with the patients compared to nurses on subjective feelings of pain/discomfort and anxiety/depression. In patients with poor cognition, the proportions of exact agreement of family caregiver–nurse pairs were all above 98% in the observable dimensions but only 37–38% in the subjective dimensions (Table 3).

Agreement of EQ-5D index

The mean EQ-5D index among the 55 patients was 0.23 ± 0.20. The mean differences in the EQ-5D index were −0.03 ± 0.14 and 0.03 ± 0.22 for patient–family caregiver pairs and patient–nurse pairs, respectively; this difference was not statistically significant (Table 4). In PMV patients with poor cognition, the average EQ-5D index assigned by family caregivers and nurses were 0.12 ± 0.10 (0–0.44) and 0.14 ± 0.11 (0–0.63), respectively. The effect size of the mean differences for these measurements was 0.13, which is small [24]. The ICC of the EQ-5D index for patient–family caregiver pairs was excellent (0.76), which seems much higher than that of the patient–nurse pairs (0.36) (Table 4).

Discussion

To our knowledge, this study is the first that validates agreement on QOL between PMV patients and their proxies (family caregivers and nurses) as measured by the EQ-5D preference instrument; in addition, these conclusions were validated in both PMV patients with good and poor cognition. Our findings demonstrate that family caregivers tended to rate all dimensions as being more severe than did patients themselves and that family caregivers' assessments were in closer agreement with patients' assessments than were those of their nurses, using either observable dimensions or subjective feelings. Moreover, agreement on the observable dimensions between family caregivers and nurses was higher (proportions of exact agreement = 98–99%) in PMV patients with poor cognition.

Our study corroborates previous investigations finding better agreement between patients and their proxies for directly observable dimensions (mobility, self-care, and usual activities) than for assessments of subjective feelings

Table 3 Frequency distribution of agreement among patients with poor cognition and their proxies for each dimension in the EQ-5D

Dimension	Family caregiver $n = 81$ (%)	Nurse $n = 81$ (%)	Family caregiver–nurse $n = 81$ weighted kappa (confidence intervals) and [proportion of exact agreement]
Mobility			
No problems	0	0	
Problems	1 (1)	1 (1)	−0.01 (−0.03–0.00)
Confined to bed	80 (99)	80 (99)	[98%]
Self-care			
No problems	0	0	
Some problems	0	1 (1)	0.00 (−0.00–0.00)
Unable to wash/dress	81 (100)	80 (99)	[99%]
Usual activities			
No problems	0	0	
Some problems	0	1 (1)	0.00 (−0.00–0.00)
Unable to perform	81 (100)	80 (99)	[99%]
Pain/discomfort			
None	16 (20)	9 (11)	
Moderate	27 (33)	45 (56)	0.05 (−0.13–0.23)
Extreme	38 (47)	27 (33)	[37%]
Anxiety/depression			
None	19 (23)	10 (12)	
Moderate	30 (37)	48 (59)	0.08 (−0.08–0.24)
Extreme	32 (40)	23 (28)	[38%]

Table 4 Differences and reliabilities of EQ-5D index measured in patients on PMV (prolonged mechanical ventilation) and their proxies, according to value systems established in the United Kingdom (UK) and United States (US)

	Mean difference[ab] ± SD (minimum–maximum)		Effect size		ICC[cd] (confidence intervals)
	US	UK	US	UK	
Patients with partial cognition capable of responding (mini-mental status examination, MMSE ≧ 15)					
Patient–family caregiver ($n = 44$)	−0.03 ± 0.14 (−0.52–0.22)	−0.04 ± 0.17 −0.39–0.37)	0.21	0.24	0.76 (0.60–0.86)
Patient–nurse ($n = 53$)	0.03 ± 0.22 (−0.60–0.50)	0.00 ± 0.23 (−0.51–0.46)	0.14	0.00	0.36 (0.11–0.58)
Family caregiver–nurse ($n = 42$)	0.07 ± 0.18* (−0.38–0.40)	0.07 ± 0.22* (−0.44–0.50)	0.39	0.32	0.49 (0.22–0.69)
Patients with poor cognition and unable to respond (MMSE <15)					
Family caregiver–nurse ($n = 81$)	0.02 ± 0.15 (−0.38–0.52)	0.02 ± 0.20 (−0.37–0.44)	0.13	0.10	0.00 (−0.22–0.20)

*$p < 0.05$

[a] Proxy minus patient score: a negative sign indicates that proxies underestimated the score

[b] Nurse minus family caregiver: a negative sign indicates that the nurses consistently scored lower than did family caregivers

[c] ICC: intra-class correlation coefficients

[d] US value system only

and mental health (pain/discomfort and anxiety/depression) [32–34]. However, family caregivers tended to rate all dimensions at a slightly higher severity than did patients themselves, while nurses gave less severe ratings compared to patients (Table 2). Family caregivers were generally allowed to stay with patients after their hospitalization in RCW institutions, which may partially explain why they were apparently able to perceive so accurately the feelings of PMV patients, with all proportions of the exact agreement above 86% for observable dimensions and 52% for subjective dimensions. In addition, no significant differences were identified between the final EQ-5D utility values from the patient–family caregiver pairs (Table 4). In contrast, only 27% of the interviewed nurses had daily contact with the patients, as they generally rotated and took days off each week (Table 1). We applied multiple regression analysis to estimate the potential effect of this determinant on the mean difference between patient–nurse pairs, but it did not show any statistical significance. Overall, the agreement within patient–family caregiver pairs is consistently closer than that of patient–nurse pairs, indicating that family caregivers may be a more suitable proxy for PMV patients in the Taiwanese culture.

In PMV patients with poor cognition, it is not surprising that both the weighted kappa (Table 3) and ICC (Table 4) were very low, because these patients were generally bedridden in RCC/RCW units, and there is almost zero variation in the observable dimensions of mobility, self-care, and usual activities. Thus, such extremely limited distributions hamper the values of weighted kappa and ICC, and we must also provide the results of proportions of exact agreement, which were as high as 37–99% (Table 3) to avoid misinterpretation.

Nonetheless, there was no statistically significant difference between the final utility values of EQ-5D from patient–family caregiver and patient–nurse pairs in PMV patients with partial cognition. Because the EQ-5D value system of Taiwan has not yet been published, we applied the values obtained from the United States and United Kingdom for sensitivity analysis [17, 22]. Although the values based on the US system seem smaller than those from the United Kingdom, they yielded similar results, apparently due to the limited variation of health states in these patients (Table 4). Thus, the nurse's rating appears as acceptable as that of a family caregiver for use as a proxy to rate the utility value of the EQ-5D in PMV patients with poor cognition, even though the ICC of these pairs was only 0.00.

A possible limitation of this study was its cross-sectional design. Although we conducted a multiple regression analysis using the utility value of EQ-5D as the dependent variable and the duration of mechanical ventilation as an independent variable in the model, there was no significant difference. Thus, we were unable to answer whether the agreement of QOL measurements between patients and proxies may change longitudinally over different time points. Another possible limitation was the 80% response rate and the degree to which our sample was representative of the population as a whole. There was no statistically significant difference in patient characteristics between respondents and non-respondents. However, because family members of 22 of the 35 non-respondents did not come to visit the patients during our 3–4 week study period, those patients might have a poorer QOL compared to that of the others. Ten family caregivers refused to be interviewed at the time of our request, as they were coping with their relative's deteriorating condition. Thus, our results might have overestimated the QOL of PMV patients. Finally, the extremely skewed responses in the objective dimensions of the EQ-5D in patients with poor cognition result in a generally low weighted kappa (Table 3), reflecting the inappropriateness of using such indicators. Thus, we have calculated the proportion of exact agreement to allow us to make a suitable inference.

Conclusions

Although the sensitivity analysis did not show any significant differences in overall utility value of QOL measurements using EQ-5D between patients on PMV and their proxies, family caregivers exhibited closer agreement with the patients than did nurses on QOL evaluation, especially on rating subjective feelings of pain/discomfort and anxiety/depression. However, there was no difference between the two proxies in the final utility values for PMV patients with poor cognition. Further research into these issues is still needed in subjects from different cultures to corroborate our findings.

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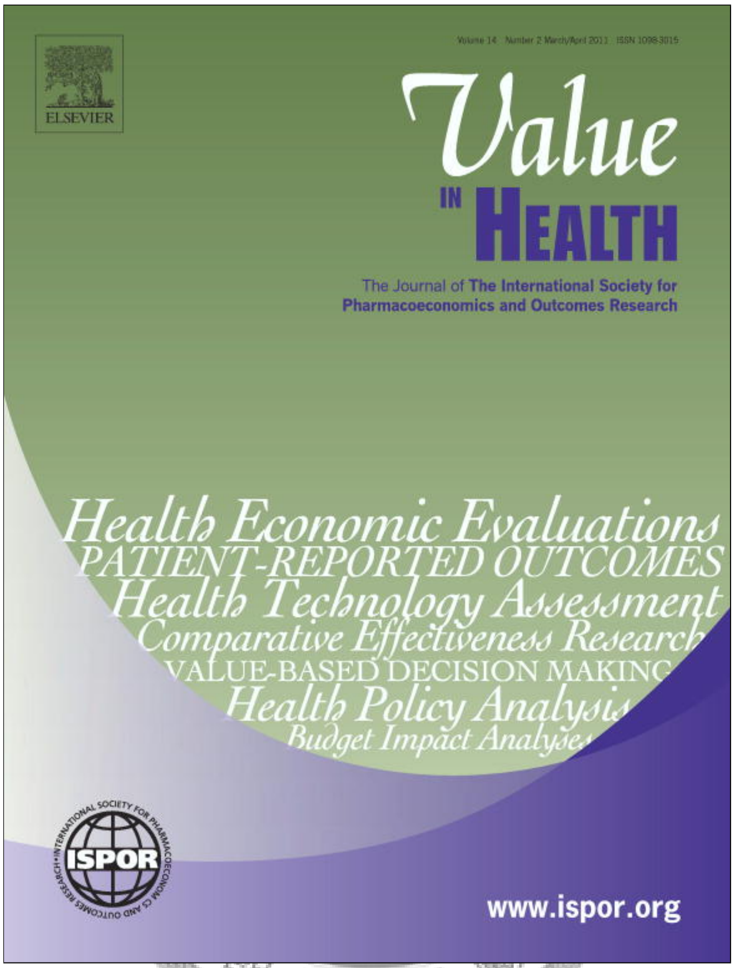
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Estimation of Quality-Adjusted Life Expectancy in Patients Under Prolonged Mechanical Ventilation

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ABSTRACT

Objectives: The purpose of this study was to estimate the quality-adjusted life expectancy (QALE) and the expected lifetime utility loss of patients with prolonged mechanical ventilation (PMV).

Methods: PMV was defined as more than 21 days of mechanical ventilation. A total of 633 patients fulfilled this definition and were followed for 9 years (1998–2007) to obtain their survival status. Quality of life of 142 patients was measured with the EuroQol five-dimensional (EQ-5D) questionnaire during the period 2008 to 2009. The survival probabilities for each time point were adjusted with a utility measurement of quality of life and then extrapolated to 300 months to obtain the QALE. We compared the age-, gender-matched reference populations to calculate the expected lifetime utility loss.

Results: The average age of subjects was 76 years old. The life expectancy and loss of life expectancy were 1.95 years and 8.48 years, respectively. The QALE of 55 patients with partial cognitive ability and the ability to respond was 0.58 quality-adjusted life years (QALY), whereas the QALEs of 87 patients with poor consciousness were 0.28 and 0.29 QALY for the EQ-5D measured by family caregivers and nurses, respectively. The loss of QALE for PMV patients was 9.87 to 10.17 QALY, corresponding to a health gap of 94% to 97%.

Conclusions: Theses results of poor prognosis would provide stakeholders evidence for communication to facilitate clinical decisions. The estimation may be used in future studies to facilitate the cost-effectiveness and reduction of the health gap.

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Introduction

The number of patients requiring prolonged mechanical ventilation (PMV) is rapidly increasing, because the improved quality of care in ICUs (intensive care units) has resulted in the long-term survival of many patients [1–3]. However, these patients often continually require respiratory care after transfer to a rehabilitation facility, skilled nursing facility, or home care, and this creates a tremendous financial burden for the insurance system and/or their families [2,3]. The financial impact is particularly heavy for countries with a national health insurance system with universal coverage of their citizens and is aggravated by the innovation of new technologies and an aging population [4]. Most of these countries have adopted economic analyses to improve overall cost-effectiveness and contain costs [5–7]. Evaluation of the cost per quality-adjusted life year (QALY) gained from different healthcare services will ensure the most cost-effective policy decision for health care.

The National Health Insurance (NHI) of Taiwan adopts a system of comprehensive coverage for various health-care services, including maintenance hemodialysis and chronic respiratory care. It was first established in 1995 and has been extended to cover more than 99% of the citizens of Taiwan [8,9]. The NHI established a Pilot Program of Ventilator Dependent Managed Care in 2002 to provide subsequent and long-term care for patients using PMV who are overcrowding the ICU. The program intended to cover medical services in the acute stage in the ICU, during weaning trials in the respiratory care center, dispatch to the respiratory care ward if weaning trials failed, and respiratory therapy in home care. Because the expense of chronic care for patients under PMV at home is generally too profound for most families, many try to keep their loved ones at the respiratory care ward for as long as possible. Thus, the reimbursement has resulted in a large financial burden for the NHI. During 2005, the total number of PMV patients who required respiratory care in the NHI of Taiwan reached 30,000 and accounted for 7.5% of the total NHI health-care expenditures, and this has now become one of the major threats to the sustainability of the NHI [10,11].

This study has considered both long-term survival and quality of life (QOL) together for PMV patients. Such a lack of prognostic data plus the families' unreasonably optimistic expectations often complicates the family-physician interaction [12], and makes it difficult to communicate among patients, their families, and health-care workers for clinical decision making before and throughout the course of installing mechanical ventilation. Therefore, the purpose of this study was to estimate the QOL utility, lifetime survival, quality-adjusted life expectancy (QALE), and expected utility loss for patients using PMV.

Methods

The cohort and survival of PMV patients

We recruited all patients who were admitted to the intensive care unit and later received care at a respiratory care center and respiratory care ward in a teaching hospital in southern Taiwan between 1998 and 2007. The recruitment criterion for PMV patients was the need for mechanical ventilation support for more than 6 hours per day for 21 days [13]. Each patient was followed from the 22nd day that he or she received PMV until they died or were censored on December 31, 2007. The Kaplan-Meier method was applied to estimate the survival function.

In general, when the patients are unable to have a normal respiration function, mechanical ventilation is installed for the support of life. It is commonly established in the intensive or critical care unit, and usually a tracheotomy is performed to provide a consistently patent airway. Even under the ventilator support, such patients did not survive for more than 1 to 3 years, but occasionally there were patients with a longer survival. Thus, lifetime survival of PMV patients (up to 300 months) was obtained using a linear extrapolation of a logit-transformed curve of the survival ratio between the PMV and an age-, gender-matched reference population generated by the Monte Carlo method from the life table of the general population of Taiwan. The detailed method and the mathematical proof under the assumption of constant excess hazard can be found in our previous reports [14–18] and are briefly summarized below. Because the collection period of PMV patients ranged from 1998 to 2007, we chose the life table of the middle year (2002) for the Monte Carlo simulation.

Survival function of the age-, gender-matched hypothetical reference population

The life tables for the general population were obtained from the vital statistics published by the Department of Statistics, Ministry of the Interior, Executive Yuan, Taiwan [19]. Because the individual survival time of the subjects in a hypothetical cohort cannot be directly derived from the life table of the general population, we used the Monte Carlo method to generate the simulated survival time of age- and gender-matched hypothetical reference subjects for each patient in the PMV cohorts. The total collection of hypothetical subjects was used as the reference population. Then, the survival curve of the reference population was obtained by applying the Kaplan-Meier method to the simulated survival times.

Cross-sectional sample of PMV patients for utility measurements of QOL

To estimate the QOL utility function for these patients, we recruited a cross-sectional sample of PMV subjects [18] who, after 21 days, continued to receive care from five institutions in Taiwan. Informed consent was obtained from every patient and/or his/her family caregiver, and the study commenced after the approval of the Institutional Review Boards (IRBs) of Chia-Yi Christian Hospital and National Taiwan University Hospital. The three local hospitals also approved the study after reviewing the approval documents of the above two major IRBs.

The utility value of the QOL for PMV patients was measured using the EuroQol five-dimensional (EQ-5D) questionnaire. It is a preference-based, generic instrument [20,21] and has been extensively used in many critically ill patients based on multi-attribute utility theory [22–24]. The five dimensions assessed by the EQ-5D are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each with three levels of severity (no problems, some/moderate problems, and severe/extreme problems). This provides a utility value that ranges from 0 to 1 based on the five-dimensional health state classification; 0 represents the worst health status and 1 represents perfect health. For subjects with basic cognition who communicated their responses and achieved a score of more than 15 on a mini-mental state examination (MMSE) [25,26], we conducted QOL measurements with the EQ-5D via direct face-to-face interview. Each individual patient was cross-sectionally measured one time on EQ-5D. When the patient's consciousness was too poor to communicate with the interviewer, family caregivers and nurses were used as proxies [27–30]. We have summarized the detailed methods of validating measurements in another study [31]. Briefly, we invited both family caregivers and nurses who directly took care of the patient to also evaluate the five dimensions of EQ-5D on the patient's behalf based on his/her understanding. The results were directly compared with the patient's own rating, which is considered the gold standard. The duration-to-date for each measurement is defined from the 22nd day after PMV to the date of the interview by the researcher. A cross-sectional sample of patients with PMV was obtained and the kernel-type smoothing method (moving average of the nearby 10%) was performed to calculate the mean QOL throughout the follow-up time period of 9 years [17,18]. The QOL value after 9 years was assumed to be the same as the end of follow-up time. We compared our results with the value systems of the United States and the United Kingdom. [21,32].

Table 1 – Demographic and clinical characteristics of patients under PMV in a cohort group to obtain the survival function and a cross-sectional sample for measurements of quality of life.

Characteristics	Cohort of PMV	Cross-sectional sample of patients under PMV
Calendar years of collection	1998–2007	2008–2009
Total number of patients	633	142
Mean age in year (SD)	76 (12)	75 (12)
% Female	45	43
Major underlying diseases and comorbidities		
% Hypertension	48	28
% Diabetes mellitus	40	25
% Cerebrovascular diseases	31	18
% Chronic obstructive pulmonary disease	27	32
% End-stage renal disease	13	11
% Asthma	7	4
% Liver cirrhosis	3	2
% Coronary artery disease	13	6
Reasons for mechanical ventilation		
% Apnea or required resuscitation	12	7
% Ventilatory failure	46	45
% Oxygenation failure	14	6
% Post operation	10	7
% Airway protection	1	1
% Others	17	34

PMV, prolonged mechanical ventilation; SD, standard deviation.

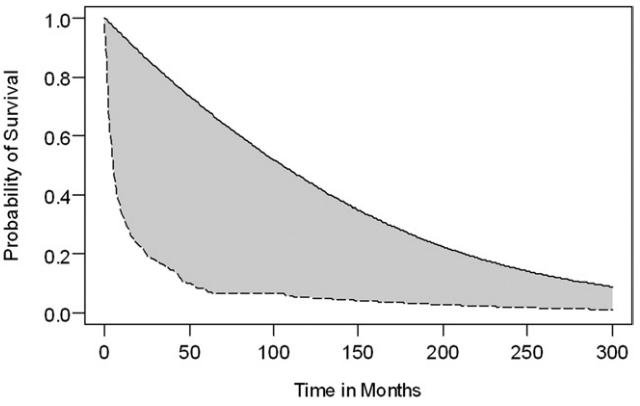

Fig. 1 – The life expectancy (area under the dotted line) and loss of life expectancy (shadowed area between the two curves) in years for 633 patients under prolonged mechanical ventilation (PMV) after extrapolation to 300 months.

Statistical analysis

Integration of survival and QOL functions, QALE, lifetime utility loss, and health gap

The lifetime survival probabilities along the duration-to-dates (or time after beginning PMV) were multiplied (or adjusted) with the QOL values measured from EQ-5D to obtain a quality-adjusted survival curve, of which the sum of the total area under this curve was the QALE with QALY as the common unit [18]. The expected lifetime utility loss for PMV patients was calculated by assuming a uniform utility of one for the age- and gender-matched reference subjects and subtracting the QALE of PMV patients [14,16,18]. In other words, based on the hazard function or vital statistics of Taiwan, we simulated survival functions of ten reference people of the same age and gender for every PMV patient and assumed that the utility of their QOL is one that would have been the QALE of each PMV patient had they not developed the condition. The health gap, usually considered an indicator of health inequality, was defined and calculated as the proportion of expected loss of lifetime utility of patients with PMV in comparison with age- and gender-matched hypothetical referents simulated from vital statistics of Taiwan [33]. To facilitate the computation, we used the MC-QAS software program built on the *R* statistical package for quality adjusted survival estimation and 300-month extrapolation, designed by Dr. Jing-Shiang Hwang, Institute of Statistical Science, Academia Sinica, Taipei, Taiwan which can be downloaded for free from the following website: http://www.stat.sinica.edu.tw/jshwang.

Results

The medical records of 633 patients who fulfilled the definition of PMV were abstracted and linked to the National

Mortality Registry of Taiwan in 2007 to obtain their survival status. Many suffered from multiple co-morbidities, including hypertension (about half), diabetes mellitus (about two-fifths), stroke, and chronic obstructive pulmonary disease (COPD), among others, as summarized in Table 1. More than half required mechanical ventilation because of ventilation failure resulting from the above multiple co-morbidities or from cardiopulmonary resuscitation, whereas about one-seventh needed such services because of chronic lung conditions, including COPD. The overall 1-year survival rate was 33%.

From 2008 to 2009 we also screened 177 patients from five institutions and enrolled 142 patients with PMV (response rate of 80%); 55 patients provided their EQ-5D ratings directly and 87 were assessed only through either family caregivers and/or nurses. The demographic and clinical characteristics of the above two groups of PMV subjects are summarized in Table 1.

The life expectancy was 1.95 years and is depicted as the area under the survival curve of PMV patients in Figure 1. The average loss of life expectancy of these patients was 8.48 years, whereas the difference between the survival curve of age- and gender-matched referents and that of PMV patients and is shown by the shadowed area in Figure 1. After adjustment for QOL utility values directly measured on 55 patients who were able to respond, the QALE was 0.58 QALY, whereas QALE of patients with poor consciousness were 0.28 and 0.29 QALY for EQ-5D measured by family caregivers and nurses, respectively. Assuming that the utility value of each referent was one throughout their lifetime, the loss of QALE for PMV patients was 9.87 QALY (upper panel of Fig. 2), whereas the results for 87 patients with poor cognition and inability to respond (MMSE$<$15) were 10.17 and 10.16 QALY for utility values measured by family caregivers and nurses, respectively. The sensitivity analysis of substituting the utility values of the United States with those from the United Kingdom did not show a significant difference in QALE between patients and their proxies and is summarized in Table 2. The health gap was 94% and 97% for patients with a partial cognition and poor cognition, respectively.

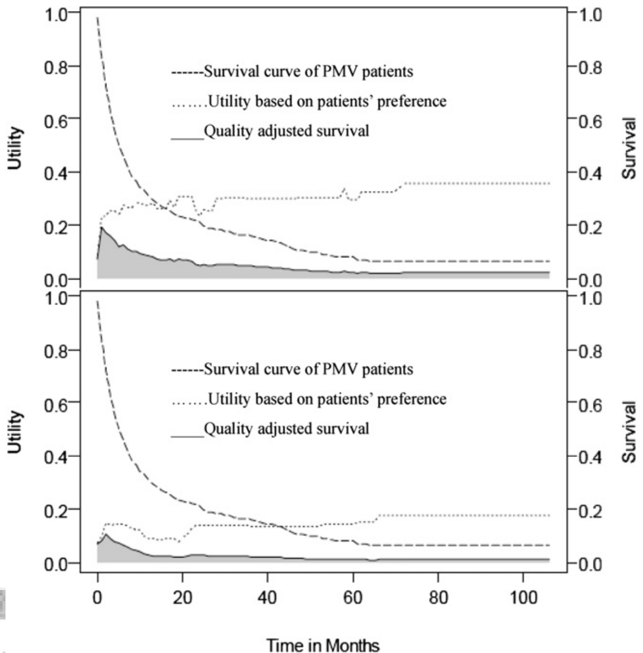

Fig. 2 – Quality adjusted survival for patients undergoing prolonged mechanical ventilation (PMV) after adjustment of survival function (N=633) with the utility values of quality of life measured with the EQ-5D. The upper and lower panels depict the results of patients' preference values (N=55) and that of family caregivers' on their behalf (N=87), respectively, with the quality-adjusted life expectancy of 0.58 and 0.28 quality-adjusted life years by summing the areas under the quality-adjusted survival curves (shaded areas).

Discussion

This study estimates lifetime survival function and quality of life in PMV patients while simultaneously obtaining the quality-adjusted life expectancy and the expected lifetime utility loss, and providing empirical evidence to facilitate discussion on health policy decision among patients, their families, health-care workers, and the policy makers. We found that the life expectancy of patients using PMV was 1.95 life years, which is less than the 2.65 life years estimated by Cox et al. [34] through Markov model simulation. Moreover, the QALE estimated by this study was only 0.28 to 0.58 QALY, which is much less than the 1.77 QALY reported previously [34]. Although investigators would usually like to compare the results from ex ante prediction with those of ex post outcome evaluation, the two studies cannot be directly compared because of major differences in the recruited subjects and measurements. Our study has a much higher proportion of patients with poor consciousness (62% vs. 30%), the patients were on PMV more than 21 days, and the patients were on average 10 years older than theirs (mean ages 76 vs. 66 years) [34,35]. Thus, our subjects had a poorer quality of life and lower 1-year survival rate (33% vs. 42%) than others [23, 34–36]. Moreover, different types of utility measurements of QOL were applied in different studies, EQ-5D versus SF-36 or quality of well-being index. Hence, the estimated QALE in our patients under PMV were lower than those reported from previous studies. We therefore recommend that future research on patients with normal or better consciousness be conducted to determine the QALE more accurately for such patients with different age and gender strata.

Given the limited resources in health care, it is inevitable that most countries with a national health insurance system must consider the comparative cost-effectiveness of their decisions on resource allocation, and the common unit of QALY that simultaneously considers both mortality and morbidity (or, survival and quality of life) has become more widely used. The National Institute for Health and Clinical Excellence in the United Kingdom [37,38] is known worldwide for such practices. However, there are still controversial issues of distributive justice in bioethics concerning potential discrimination against the aged and disabled [39,40]. Daniels proposes in the

Table 2 – QALE (in years) and expected lifetime loss of utility for patients under PMV based on different value systems of EQ-5D and patient's cognition for sensitivity analysis.

Categories	QALE (SE)		Expected lifetime loss of utility (SE)	
Country of value system for EQ-5D	UK	US	UK	US
Patients with partial cognition and ability to respond (MMSE≧15, n=55)				
QOL measured by patients (n=55)	0.74 (0.13)	0.58 (0.09)	9.73 (0.13)	9.87 (0.09)
QOL measured by family caregivers (n=44)	0.67 (0.15)	0.61 (0.18)	9.80 (0.16)	9.84 (0.19)
QOL measured by nurses (n=53)	0.70 (0.16)	0.64 (0.15)	9.77 (0.11)	9.81 (0.15)
Referents (age- and gender-matched)	10.47 (0.02)	10.45 (0.02)	—	—
Patients with poor cognition and inability to respond (MMSE<15, n=87)				
QOL measured by family caregivers (n=81)	0.44 (0.09)	0.28 (0.05)	9.98 (0.13)	10.17 (0.06)
QOL measured by nurses (n=81)	0.43 (0.09)	0.29 (0.05)	9.99 (0.09)	10.16 (0.05)
Referents (age- and gender-matched)	10.42 (0.02)	10.45 (0.02)	—	

MMSE, mini-mental state exam; PMV, prolonged mechanical ventilation; QALE, quality-adjusted life expectancy; QOL, quality of life; SE, standard error.

principle of distributive justice that everyone is entitled to obtain health care up to their "normal life span," if possible [39], and this is adopted in the calculation of a health gap proposed in the summarization of the population health [33]. The health gap was 94% and 97% for patients with a partial cognition and poor cognition, respectively, indicating that these patients are more disadvantaged and deserve more resources based on the principle of justice. Therefore, we recommend that more efforts be implemented to improve the long-term survival and QOL for PMV patients with different underlying causes or co-morbidities to improve the efficacy of such a treatment if the cost is paid by the patients themselves or their private health insurances. If, however, the expense of PMV is paid by national health insurance, the results of this study can facilitate a more reasonable decision among all stakeholders according to the principles of equity and efficiency. For example, are we willing to spend more resources on PMV or child health, vaccinations, and preventive care, among others? Without the above data, the task of making health decisions is generally difficult.

In Asian countries (including Taiwan), where patients and their families are not accustomed to preparing their wills early in life or signing "do not resuscitate" documents before they are critically ill, the estimates of QALE for patients with PMV are relevant and can be the opening to begin a dialogue between all stakeholders and the public. The results provide the first evidence to sound the wake-up call for the public to contemplate and openly discuss the principles of health resources distribution for the national health insurance on PMV care.

Our study has the following limitations. First, the validity of the QOL measurement for critically ill patients with an impairment of cognition or even unconsciousness must be addressed. To resolve this difficulty, we conducted a survey of the patient's proxies that included both family caregivers and nurses who directly took care of the patient, which was reported in other studies [27–29,34]. The results are summarized in a separate report directly comparing the EQ-5D values of 55 patients with those rated by their family caregivers and nurses [31]. Because EQ-5D contains only two dimensions that require subjective rating, namely, pain/discomfort and anxiety/depression, we found minor differences of the final EQ-5D values between the patient-caregiver pairs and patient-nurse pairs, −0.03±0.14, and 0.03±0.22, respectively. The results enabled us to stratify these patients according to the severity of their cognitive ability deficits and to calculate the quality-adjusted life expectancy as a sensitivity analysis, which showed that the difference between patients with good and poor consciousness is less than 0.30 QALY (Table 2). Although our sample size was too small for us to further stratify into more categories according to age and gender, it seemed that the difference might not be large for patients with poor consciousness. Second, we assumed a uniform utility of one for the age- and gender-matched reference subjects that over-estimated the lifetime utility of the general population and also the expected lifetime utility loss of PMV patients. However, because such an assumption is uniformly applied, the bias was minimized when we calculated the health gaps for different health conditions. Third, during the lifetime extrapolation of QOL function it was assumed that the patients remained at the same level of QOL near the end of follow-up. Such an assumption could have resulted in an overestimation because the actual QOL might gradually decline as the patient ages. Fourth, the accuracy of the estimation of QALE would have improved if we had obtained quality-of-life measurements during the follow-up of every patient in the PMV cohort. Unfortunately, we were unable to conduct this study prospectively. Thus, we simply took another consecutive, cross-sectional sample of 142 PMV patients with different duration-to-dates and applied a smoothing method for the estimation of lifelong QOL function. We have demonstrated through simulation that a random sample of more than 50 subjects would be adequate for the above estimation, or, the relative bias would be less than 5% [18]. In fact, the PMV cohort to estimate survival function and the cross-sectional sample of subjects under PMV for QOL measurements seemed comparable in age, gender, and Glasgow Coma Scale (Table 1). Fifth, we used the age- and gender-matched general population as the reference group to estimate the loss of QALE and health gap for PMV patients.

Because patients with PMV usually cannot survive for more than 1 day without ventilation support, it is almost impossible or extremely difficult to collect another group of patients under the same condition but without mechanical ventilation. However, future studies are planned that will collect more PMV cases and stratify them by different co-morbidities and/or underlined diseases to determine if their survival and QOL are different to further improve the cost-effectiveness for such care. Finally, because each country may have different quality of care, and hence, different survival and QOL functions, the generalization of the results from this study to other nations may be limited.

Conclusions

The life expectancy of an average 76-year-old patient under PMV was about 1.95 years in Taiwan, which amounts to 0.58 QALY (partial consciousness) and 0.28 QALY (poor consciousness) after an adjustment for quality of life measured by EQ-5D. The estimate is useful to facilitate discussions among patients, their families, and health-care workers for clinical decision making early and throughout the course of installing mechanical ventilation. Moreover, the results can also serve as a starting point for a public dialogue on resource allocation of the NHI on critical care, aging, and palliative care. Future studies should further integrate medical cost into the estimation of the cost per QALY gained together with consideration of reduction of the health gap to preserve health equality.

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CRITICAL CARE

RESEARCH Open Access

Life expectancies and incidence rates of patients under prolonged mechanical ventilation: a population-based study during 1998 to 2007 in Taiwan

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Abstract

Introduction: The present study examined the median survival, life expectancies, and cumulative incidence rate (CIR) of patients undergoing prolonged mechanical ventilation (PMV) stratified by different underlying diseases.

Methods: According to the National Health Insurance Research Database of Taiwan, there were 8,906,406 individuals who obtained respiratory care during the period from 1997 to 2007. A random sample of this population was performed, and subjects who had continuously undergone mechanical ventilation for longer than 21 days were enrolled in the current study. Annual incidence rates and the CIR were calculated. After stratifying the patients according to their specific diagnoses, latent class analysis was performed to categorise PMV patients with multiple co-morbidities into several groups. The life expectancies of different groups were estimated using a semiparametric method with a hazard function based on the vital statistics of Taiwan.

Results: The analysis of 50,481 PMV patients revealed that incidence rates increased as patients grew older and that the CIR (17 to 85 years old) increased from 0.103 in 1998 to 0.183 in 2004 before stabilising thereafter. The life expectancies of PMV patients suffering from degenerative neurological diseases, stroke, or injuries tended to be longer than those with chronic renal failure or cancer. Patients with chronic obstructive pulmonary disease survived longer than did those co-morbid with other underlying diseases, especially septicaemia/shock.

Conclusions: PMV provides a direct means to treat respiratory tract diseases and to sustain respiration in individuals suffering from degenerative neurological diseases, and individuals with either of these types of conditions respond better to PMV than do those with other co-morbidities. Future research is required to determine the cost-effectiveness of this treatment paradigm.

Introduction

The number of patients who require prolonged mechanical ventilation (PMV) is rapidly increasing worldwide, apparently due to aging, a greater number of co-morbidities, and the increasing availability and effectiveness of this new technology [1-3]. The fact that many patients require continued respiratory care after being transferred into a rehabilitation facility creates a tremendous financial burden [3,4]. Furthermore, there is often a gap between families' unreasonably optimistic expectations and clinicians' professional judgement. This gap frequently results in difficulties arriving at consensus clinical decision-making [5]. In many cases, these challenges are not easily resolved. These issues are exacerbated by the lack of evidence regarding expected survival times for different subgroups of patients, especially for those suffering from multiple co-morbidities.

The National Health Insurance (NHI) of Taiwan has implemented a system of comprehensive coverage for various healthcare services, including maintenance

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haemodialysis and chronic respiratory care. The NHI was first established in 1995 and has been extended to cover over 99% of the citizens of Taiwan [6,7]. In 1998, the Bureau of the NHI drafted a prospective payment programme to encourage integrated care for mechanically ventilated patients, which was implemented in July 2000 [8]. After several revisions, this programme ultimately covered mechanical ventilator care in the following settings: ICUs (acute stage, <21 days), respiratory care centres (a subacute stage for weaning training, up to 42 days), respiratory care wards (a chronic stage or long-term care), and homecare services (a stable stage during which the patient is cared for directly by family caregivers). The rising number of patient-days for mechanical ventilation usage during 1997 to 2004 increased the financial burden of the NHI [9].

Similar to the case in western countries [5], discrepancies frequently exist in Taiwan between a family's initial expectations and their physician's professional judgement. These discrepancies impair communication among patients, their families, and healthcare workers for clinical decision-making before and throughout the course of installing mechanical ventilation. There is thus a need to estimate the incidence rates and life expectancies for PMV patients with various diagnoses. Accurate prognoses are essential to propose and establish a sustainable national policy and to facilitate communication among different stakeholders. To examine the above issues, we collected a random sample from the national database and compared age-specific incidence rates, cumulative incidence rates (CIRs), median survival, and life expectancies of PMV patients stratified according to their underlying diseases.

Materials and methods

Study population, datasets, and calculation of age-specific and cumulative incidence rates

The present study was approved by the Institutional Review Board of the National Taiwan University Hospital, which also waived the requirement for obtaining informed consent because the study was conducted on a secondary database with encrypted identification numbers. The reimbursement data file obtained from the NHI of Taiwan was transformed into a research database by the National Health Research Institutes (in Chunan, Taiwan) [10]. The identification numbers of all individuals in the reimbursement data file were encrypted to protect their privacy. These files contained detailed demographic data (including birth date and sex) and information regarding the healthcare services provided for each patient, including all payments for outpatient visits, hospitalisations, prescriptions, diagnoses, and intervention procedures. The data for each inpatient hospitalisation included up to five diagnoses, which were coded according to the International Classification of Diseases (Ninth Revision) and the date of each prescription or procedure. In total, 8,906,406 individuals had undergone invasive or non-invasive respiratory care at least once during the period from 1997 to 2007. This number corresponds to approximately 29.4% of the entire insured population. Because the government has established guidelines stating that no more than 10% of all data can be drawn for research, we applied for a random sample of these patients with a 3.4:1 ratio and enrolled subjects who had undergone mechanical ventilation for longer than 21 days.

According to the definition of PMV in Taiwan [8], we included patients over the age of 17 who had undergone either invasive or non-invasive mechanical ventilation, with negative or positive pressure ventilators for at least 21 consecutive days in the ICU or the respiratory care centre. To ensure that all of the patients were incident cases, we excluded all prevalent cases found in 1997 and began the collection in 1998, as illustrated in Figure 1. The calendar year-specific and age-specific incidence rates were determined by taking the number of new cases of PMV patients in that stratum, multiplying by the sampling factor of 3.4, and then dividing the resulting value by the number of individuals within the specific stratum obtained from the census of the Ministry of the Interior in Taiwan [11]. The CIR (cumulative incidence rate) formula was calculated as follows [12]:

$$\mathrm{CIR} = 1 - \exp[-\Sigma_i\,(\mathrm{IR}_i)\,(\Delta t_i)]$$

where IR_i represents the age-specific incidence rate and Δt_i indicates the range of each age stratum. We calculated the $\mathrm{CIR}_{17\ \mathrm{to}\ 85}$, which estimates the likelihood that an average person in Taiwan would require PMV assuming that he or she lives to the age of 85.

Categorisation of patients for estimation of life expectancies

All recruited subjects were followed until the end of 2007 to determine whether they were alive, deceased, or censored. Because patients who had undergone PMV usually suffered from a combination of multiple comorbidities and five major diagnoses can be retrieved for each PMV patient prior to and closest to the first day, we developed a strategy to identify different homogeneous groups to make more accurate estimates of life expectancy.

First, we excluded specific categories with extremely low frequencies, including HIV infection (n = 27) and complications during pregnancy/childbirth/perinatal period (n = 240). Second, people with major diagnoses that may cause premature mortality were stratified and analysed separately, including cancer, end-stage renal

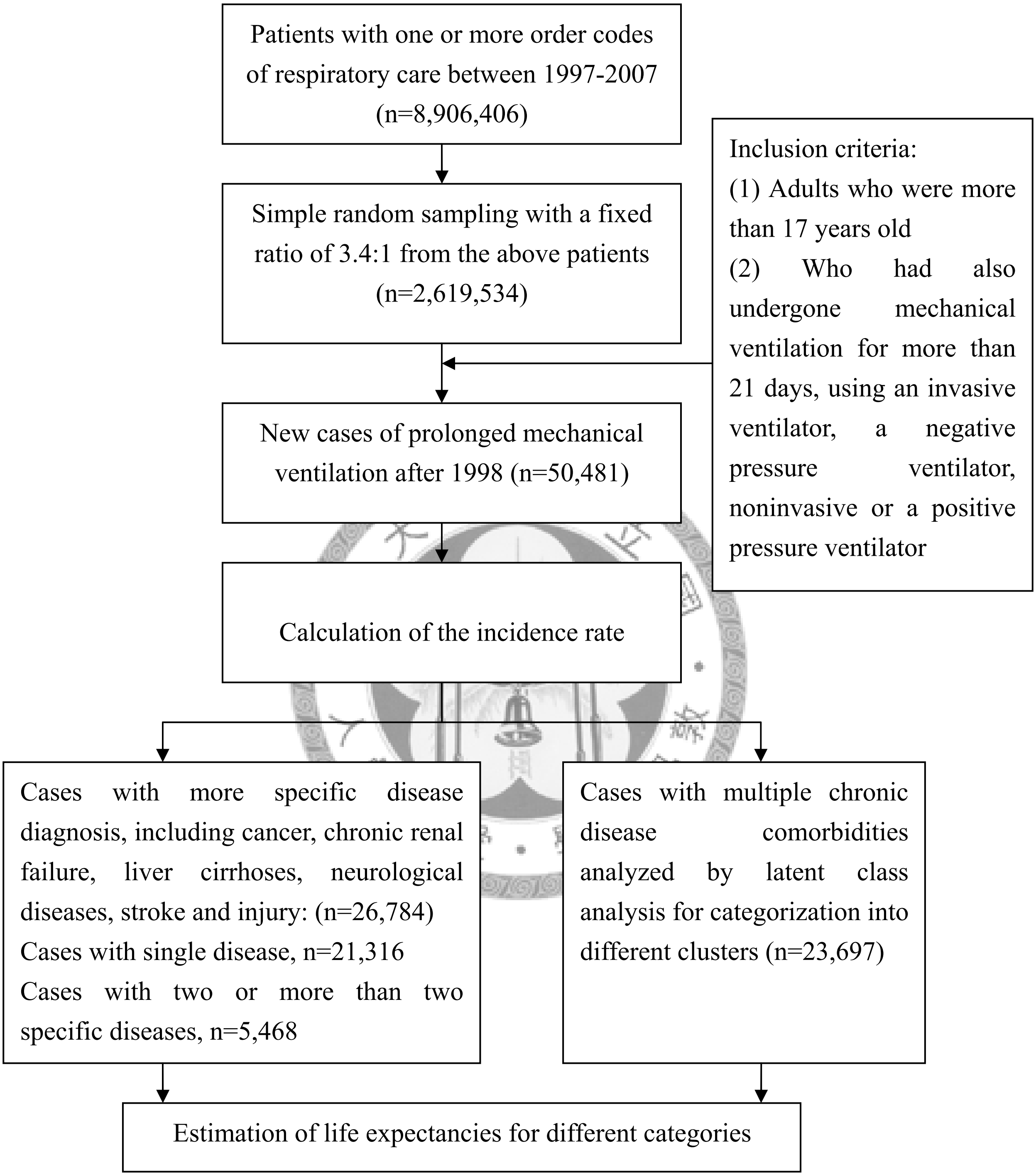

Figure 1 **Flow chart of the selection process used for the study cohort**.

disease, liver cirrhosis, multiple sclerosis or degenerative neurological diseases, Parkinson's disease, and injury or poisoning, as each group shares major common characteristics that predict mortality. Third, because the vast majority of patients suffered from a combination of multiple chronic diseases that may cause premature mortality, such as diabetes mellitus, coronary and/or heart failure, hypertension, respiratory system and/or urinary tract infections, acute renal failure, septicaemia with and without shock, and so forth, we conducted latent class analysis (LCA) for these cases to categorise them into clusters or specific homogeneous groups for estimations of life expectancies. During this process, we grouped several closely related diagnoses together and converted their original International Classification of Diseases (Ninth Revision) codes into Clinical Classifications Software codes [13] so that sufficient numbers could be obtained for survival analysis. Following the above direction, the International Classification of Diseases (Ninth Revision) codes for septicaemia included 0031, 0202, 0223, 0362, all subcategories of 038, and 7907 (bacteraemia); those for shock included all subcategories under code 785.

Statistical analysis

Binary and categorical variables were summarised using frequency counts and percentages. Continuous variables that were distributed normally are presented as means.

Latent class analysis

To determine the underlying causes that were more likely to lead to PMV, we applied LCA to group separate co-morbidity diagnoses into no more than 10 clusters of in-patients who had undergone PMV. Because pneumonia and respiratory failure are the most common reasons for mechanical ventilation, these conditions were not included in this model. The analysis resulted in an LCA model consisting of 32 broad diagnosis categories, which included chronic diseases that had been previously classified into 260 categories by Clinical Classifications Software.

LCA assumes that responses are conditionally independent within classes after accounting for class membership [14]. In other words, LCA allows for the grouping of the PMV patients into several relatively homogeneous clusters of diagnosis patterns. In constructing the model, each cluster or class was named after the major disease (that is, with the highest prevalence or likelihood) present within each age strata.

Akaike Information Criteria were used to assess the goodness of fit of the model [15]. Lower Akaike Information Criteria statistics were considered to indicate a better statistical fit of the model to the data. If any single category exhibited a prevalence approaching 100% for a given condition across different age groups, then we assumed that these conditions could be reclassified into groups with specific diseases, and life expectancy estimations were conducted separately. Throughout this process, we found that only stroke could be further separated from the groups of multiple co-morbidities, and thus the life expectancy estimation for stroke patients was performed independently. SAS statistical software (version 9.1; SAS Institute, Cary, NC, USA) and R statistical software (version 2.10.1; R Foundation for Statistical Computing, Vienna, Austria) were used for the data analyses.

Estimation of life expectancy

Each new patient who fulfilled the definition of PMV was followed beginning on the first day of PMV treatment and continuing until he/she was deceased or censored on 31 December 2007. The median survival, or the time at which only one-half of the patients within a given category were still alive, was estimated by the Kaplan-Meier method. In general, most patients did not survive longer than 1 to 3 years, although some patients did exhibit a longer survival time. All patients survived the initial 21 days of treatment by mechanical ventilation, and the survival times reported here exclusively refer to survival duration thereafter. The lifetime survival of PMV patients (up to 300 months when excluding those older than 85 years) was thus obtained using a linear extrapolation of a logit-transformed curve of the survival ratio between the PMV and an age-matched and gender-matched reference population generated by the Monte Carlo method from the life table of the general population of Taiwan. The detailed method and mathematical proof assuming a constant excess hazard have been described in our previous reports [16-20]. To facilitate the computation we used ISQoL, a software program that was built based on the *R* statistical package for lifetime expectancy estimation and 300-month extrapolation (excluding those older than 85 years) and can be downloaded for free [21].

Validation of the extrapolation method for survival functions

Empirical PMV data from the National Health Research Institutes provided us with an opportunity to validate the actual performance of our semiparametric method of estimation. We therefore selected subcohorts of patients beginning on the first day that they received PMV between 1998 and 2001. We assumed that these cohorts were only followed until the end of 2001 and then extrapolated these results to the end of 2007. We compared our predictions with the Kaplan-Meier estimates of the direct follow-ups from 1998 to 2007. Assuming that the Kaplan-Meier estimates are the gold standard, we calculated the relative biases for subcohorts stratified by different underlying diseases and co-morbidities [22]. The relative biases were computed to compare the differences in values between the Kaplan-Meier estimates and the Monte Carlo extrapolation method.

Results

Basic characteristics of the prolonged mechanical ventilation cohort

A total of 50,481 new patients with PMV were included during the study period (40% female, mean age 72 ± 14.5 years, median survival 0.37 years, and overall life expectancy 2.68 years). If we counted only the primary diagnosis (out of a maximum of five diagnoses) for each patient, the top five primary diagnoses were acute respiratory failure (15%), pneumonia (12%), intracerebral haemorrhage (5%), septicaemia (3%), and chronic airways obstruction (2%). The tracheotomy rate was 60.1%, which reflects the ethnic Chinese cultural tradition that typically avoids additional traumatic wounds if a patient is expected to pass away soon.

Trends of age-specific incidence rates and cumulative incidence rates over time

After the NHI began to reimburse long-term usage of mechanical ventilation to relieve the congested intensive care ward in 1998, the incidence rate started to rise and showed an increased trend with older age (Table 1). In the groups aged 65 to 74 years, 75 to 84 years, and older than 85 years, increased incidence rates of 76%, 88%, and 119%, respectively, were observed from 1998 to 2004, followed by a slight drop after 2005. The CIR (17 to 85 years) increased from 0.103 in 1998 to 0.183 in 2004 and then decreased to 0.145 in 2007.

Life expectancies of prolonged mechanical ventilation patients with specific underlying diseases

The median survival and life expectancies of PMV patients with different diseases are summarised in Table 2. Although median survival for most categories was <1 year, many patients showed life expectancies longer than 2 to 3 years, indicating that some patients survived relatively long periods of time. The median survival and life expectancies of PMV patients with degenerative neurological disease, stroke, or injuries were generally longer than those with chronic renal failure or cancer. When a patient contracted both cancer and chronic renal failure, the median survival durations and life expectancies were the shortest. Patients with stroke were initially included in the LCA because of the presence of multiple co-morbidities, but a distinctive category of 100% prevalence of stroke consistently appeared across different age strata. We therefore separated this group and estimated the associated life expectancies for different age strata, as summarised in Table 2.

Life expectancies of age-specific clusters in prolonged mechanical ventilation patients with multiple co-morbidities

Among the 23,697 PMV patients with multiple co-morbidities, the latent class model usually yielded three or four clusters, including heart diseases, septicaemia/shock, chronic obstructive pulmonary diseases, and/or others (for example, urinary tract infections), as summarised in Table 3. Diabetes mellitus seemed to be the most frequent co-morbid disease among all clusters because the prevalence rates were all above 14.5%. The life expectancy and median survival of PMV patients with chronic obstructive pulmonary disease (COPD) were generally longer than those of other clustered groups, especially those with septicaemia/shock. This trend continued until the age of 85, after which PMV patients with different underlying co-morbidities seem to show similar outcomes.

Validation results of the extrapolation method

The results obtained to validate our semiparametric method show that the relative biases were all below 20%. Among them, the relative biases of most PMV patients with a specific diagnosis ranged between 0.9 and 5.5%. Stroke patients were an exception and usually suffered from other co-morbidities. Patients with a combination of different diseases (or clusters) appeared less likely to fulfil the assumption of a constant excess hazard completely and resulted in greater relative biases, perhaps because they represent a relatively heterogeneous patient population. Nonetheless, the absolute differences between our estimates and those obtained using the Kaplan-Meier method were all below 0.25 life-years, except for the 65-year-old to 74-year-old multiple co-morbidity categories, which showed an absolute difference of 0.39 life-years.

Table 1 Age-specific incidence rates (per 100,000 person-years), and CIR of patients under prolonged mechanical ventilation

Age group (years)	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
Number of new cases	9,296	12,651	12,913	15,660	17,731	19,737	21,818	21,692	20,414	19,723
17 to 34	5.1	6.1	5.5	5.8	6.1	8.4	9.9	9.2	9.4	9.9
35 to 44	10.1	10.8	11.8	14.5	14.4	15.4	19.2	17.4	19.8	18.1
45 to 54	21.8	33.3	29.3	32.4	37.2	42.0	40.5	43.5	39.5	39.7
55 to 64	78.2	101.1	92.2	102.5	111.6	118.9	129.6	119.8	101.7	93.0
65 to 74	224.0	296.5	284.5	329.2	361.9	379.8	393.9	369.2	331.8	306.4
75 to 84	622.0	817.2	814.6	967.2	1,045.5	1,072.3	1,166.4	1,036.0	1,004.6	909.2
≥85	1,182.0	1,536.0	1,702.6	2,064.1	2,253.0	2,563.9	2,584.0	2,554.0	2,161.0	2,046.0
CIR	0.103	0.133	0.132	0.153	0.165	0.173	0.183	0.170	0.159	0.145

CIR, cumulative incidence rate (aged 17 to 85 years).

Table 2 Demographic characteristics and survival of patients undergoing prolonged mechanical ventilation stratified by different underlying diseases

	Number of cases	Mean age (SD)	Female (%)	Median survival (years)	Life expectancy (SE) (years)
Cases with single specific disease	21,316	69 (15)	38	0.35	3.40 (0.09)
Cancer	5,367	70 (14)	33	0.17	1.51 (0.13)
Chronic renal failure	2,032	73 (12)	51	0.78	1.36 (0.16)
Liver cirrhosis	1,478	65 (17)	35	0.19	3.59 (0.33)
Multiple sclerosis or degenerative nervous system conditions	378	65 (17)	39	0.89	4.05 (0.64)
Parkinson's disease	341	79 (7)	36	0.85	2.06 (0.30)
Stroke	6,765	70 (13)	42	0.72	3.38 (0.15)
Aged <64 years	1,955	53 (9)	35	1.65	5.21 (0.39)
Aged 65 to 74 years	1,818	70 (3)	43	0.77	2.98 (0.17)
Aged 75 to 84 years	2,176	79 (3)	44	0.56	2.09 (0.13)
Aged >85 years	816	88 (3)	54	0.39	1.68 (0.13)
Intracranial and/or spinal cord injury or poisoning	4,955	65 (19)	34	1.06	6.27 (0.24)
Aged <64 years	1,949	45 (14)	26	6.20	10.20 (0.49)
Aged 65 to 74 years	1,116	70 (3)	39	0.82	3.77 (0.22)
Aged 75 to 84 years	13,66	79 (3)	35	0.47	2.67 (0.19)
Aged >85 years	524	88 (3)	48	0.33	1.82 (0.13)
Cases with more than two specific diseases	4,772	68 (15)	39	0.32	2.96 (0.13)
Cancer and chronic renal failure	165	71 (11)	44	0.14	1.21 (0.45)
Cancer and others	1,609	70 (14)	35	0.19	1.88 (0.22)
Chronic renal failure and others	743	70 (13)	50	0.21	1.71 (0.28)

SD, standard deviation; SE, standard error of the mean.

Table 3 Clusters of different co-morbidities categorised by latent class analysis in patients with prolonged mechanical ventilation

	Age <64 years (*n* = 3,520)				Age 65 to 74 years (*n* = 5,397)			Age 75 to 84 years (*n* = 9,747)				Age >85 years (*n* = 5,033)		
	Class 1	Class 2	Class 3	Class 4	Class 1	Class 2	Class 3	Class 1	Class 2	Class 3	Class 4	Class 1	Class 2	Class 3
	Heart disease	**SP/ shock**	**UTI/ SP**	**COPD/ other**	**Heart disease**	**SP/ shock**	**COPD/ other**	**Heart disease**	**SP/ shock**	**COPD/ other**	**Respiratory disease**	**Heart disease**	**SP/ shock**	**COPD/ other**
Number of cases	616	919	197	1,788	1,074	1,824	2,499	1,404	2,856	4,142	1,345	870	1,359	2,804
Prevalence of co-morbidity (%)														
Septicaemia	11.3	62.9	72.2	6.7	10.6	66.1	5.5	11.8	72.8	11.0	7.2	10.2	79.1	11.7
Diabetes mellitus	35.5	26.8	26.1	19.7	39.7	26.1	26.5	27.1	20.5	22.6	17.2	18.6	14.5	14.6
Hypertension	17.9	4.9	9.8	8.3	20.8	6.8	13.9	16.1	4.8	17.3	12.5	15.4	3.3	15.2
AMI/coronary atherosclerosis	39.9	3.9	2.3	2.4	43.9	4.6	5.2	42.8	5.5	6.6	4.0	42.8	5.6	4.0
COPD	6.5	3.2	0.5	17.9	11.0	11.0	33.9	18.2	12.4	39.6	29.6	24.9	12.7	33.0
Other respiratory disease	21.8	23.7	13.8	30.1	22.3	18.1	26.7	20.9	17.2	0	100	24.6	19.4	25.9
Acute renal failure	12.2	20.6	9.5	4.8	12.7	16.4	4.5	12.1	16.7	4.2	5.3	8.7	15.2	5.6
UTI	5.3	0	100	14.8	5.7	25.1	21.1	11.7	28.0	24.3	21.1	16.1	30.6	29.0
Shock	11.2	39.6	33.1	2.7	10.3	39.1	2.7	8.9	38.5	4.9	3.7	7.3	41.6	5.0
Heart failure	42.2	3.2	2.6	2.4	37.0	5.8	4.8	50.1	7.2	7.7	7.4	50.5	8.3	7.7
Median survival (years)	0.80	0.34	0.88	1.64	0.39	0.23	0.55	0.29	0.21	0.95	0.38	0.32	0.20	0.35
Life expectancy (years) (SE)	5.09 (0.60)	4.51 (0.49)	4.82 (1.49)	5.25 (0.37)	2.55 (0.21)	2.14 (0.13)	2.56 (0.13)	1.86 (0.23)	1.66 (0.10)	2.12 (0.07)	2.18 (0.17)	1.48 (0.12)	1.12 (0.07)	1.52 (0.05)

AMI, acute myocardial infarction; COPD, chronic obstructive pulmonary disease; SE, standard error of the mean; SP, septicaemia; UTI, urinary tract infections.

Discussion

To our knowledge, this is the first study to analyse a nationally representative PMV dataset to estimate the incidence rates, CIR, and life expectancies stratified by age and different clusters of diagnoses. Our findings showed that new cases of PMV increased significantly from 9,296 to 21,818 between 1998 and 2004. The age-specific incidence rates increased as people grew older, a result consistent with previous reports from scholars in the United States and Canada [1,2,4,23]. The highest age-specific incidence rate of PMV was observed in patients older than 85 years in Taiwan, however, and this rate was approximately four to five times higher than those reported in the United States [24]. We attempted to quantify the lifetime risk of PMV by calculating the $CIR_{17\ to\ 85}$, which increased from 0.103 to 0.145 between 1998 and 2007 (Table 1). This finding implies that an adult person in Taiwan who lives until the age of 85 has a 10 to 15% chance of requiring PMV. Given the resource-intensiveness of PMV, this issue requires special attention. When the Bureau of the NHI of Taiwan began to audit the quality of the integrated respiratory care system in 2003, including the rates of successful weaning, readmission, and nosocomial infection, the incidence of PMV appeared to stabilise and decreased slightly, as summarised in Table 1.

In the past, there has been a general lack of data regarding the life expectancies associated with different diagnoses for patients undergoing PMV. This has made it difficult for stakeholders to reach consensus clinical decisions regarding optimal treatment strategies. The issue becomes even more complicated when payment is provided via NHI or a third party. It is understandable that the patient and his/her family always expect successful weaning and good recovery, even after longer than 21 days of continuous mechanical ventilation or PMV. According to our previous study, however, most patients undergoing PMV survive only approximately 1.5 to 2 years, and approximately 62% of them suffer from cognitive impairments and poor quality of life. Accounting for these factors results in an overall quality-adjusted life expectancy of only 0.3 to 0.4 and 0.6 to 0.7 quality-adjusted life-years [25,26]. The present study therefore further provided crucial estimates of the median survival and life expectancies of patients undergoing PMV with different diagnoses or co-morbidities, as summarised in Tables 2 and 3. Table 2 shows that the life expectancies were shortest for PMV patients with chronic renal failure and cancer or any condition co-morbid with them, followed by Parkinson's disease and stroke. In contrast, the life expectancies for degenerative neurological diseases, liver cirrhosis, injuries, and poisonings were >3.6 years. When stratified by age categories, the median survival and life expectancies for PMV patients older than 85 years were <4.6 months and <21.8 months, respectively, which were also observed for all of the different types of co-morbidities (Tables 2 and 3). The above figures call into question the cost-effectiveness of current policies and should be considered by policy-makers and the public in discussions regarding the bioethics of PMV care, especially given the limited resources of the NHI in Taiwan. Although more and more countries have tried to implement the principle of universal coverage in their national health insurance plans [27], our results provide data highlighting the needed evidence for developing strategies of sustainable management.

Although previous studies have shown similar characteristics of multiple co-morbidities in PMV patients, these reports did not stratify patients into special clusters [1,9,24,28]. The LCA showed that the underlying co-morbidities associated with PMV could be largely classified into the major categories of heart diseases, septicaemia/shock, and COPD based on the high prevalence of each cluster. Overall, LCA indicates that the life expectancies generally decreased with older age. In particular, we found that approximately 50% of the PMV patients with a combination diagnosis of septicaemia and shock usually survived <4 months, and their life expectancies were usually shorter than those determined for the other clusters within the same age stratum. The generally longer survival time of PMV patients with COPD corroborated the hypothesis that the establishment of mechanical ventilation provides more direct access for clinicians to solve problems coming from the respiratory tract, while patients with other underlying diseases may not be improved significantly unless their underlying disorders were also resolved. This advantage disappeared in individuals over 85 years of age because a high proportion of these COPD patients also suffered from other major diseases, including urinary tract infection (29%) and other respiratory diseases (26%), as shown in Table 3.

Our study has several limitations. First, the database did not contain any information regarding the severity and/or actual clinical data of the PMV patients. We were therefore unable to further stratify these patients. Because they were all under PMV care for longer than 21 days, however, all of the patients were associated with extremely severe conditions, which resulted in a very short life expectancy and suggested that 10 years of follow-up time would be usually sufficient. Second, because the recorded diagnoses must fulfil all of the reimbursement regulations of the NHI, it is possible that some diagnoses are over-represented because they were more easily reimbursed. However, the NHI of Taiwan has offered a list of 30 major categories of catastrophic illnesses that are exempt from partial co-payments, and each has its specific diagnostic criteria to prevent any abuse [29]. For example, all types of malignant neoplasm do not require co-payments, and evidence of histopathology and/or cytology is generally required for diagnoses of cancer. A diagnosis of end-stage renal disease requires documentation of chronic kidney disease with an irreversible creatinine level >8 mg/dl, or creatinine level >6 mg/dl with diabetes mellitus as a comorbid condition [30]. There are therefore strict criteria for almost all of the major diagnoses listed in Table 2. The potential selection bias for the common diseases listed in Table 3 is probably minimal because the 43 broad categories were collapsed from the 260 categories of Clinical Classifications Software codes [13], and LCA ensured that each category was as homogeneous as possible.

Conclusions

The number of PMV patients in Taiwan has increased during the past decade. Patients with different underlying diseases showed different median survival and life expectancies. The establishment of mechanical ventilation directly targets problems of the respiratory tract and provides sustainable ventilation, which may improve the survival of patients with COPD or degenerative neurological diseases more than those with other underlying causes such as septicaemia/shock, heart failure, cancer, or end-stage renal disease. The advantages of PMV seem to decrease for the older patient, however, especially those aged over 85. The results also call for further evaluation of the cost-effectiveness and bioethics of such care in Taiwan, and highlight the need for early planning of resource allocation in any system of health insurance with universal coverage.

Key messages

- The number of new patients undergoing treatment with PMV has increased rapidly during the past decade in Taiwan.
- The life expectancies of PMV patients with degenerative neurological diseases, stroke, or injuries/poisoning as their primary co-morbidity seemed to survive longer than those with chronic renal failure or cancer, or a co-morbidity with them.
- Among PMV patients with multiple co-morbidities, those with COPD as the major underlying comorbidity seem to survive longer than patients with other co-morbidities, perhaps because this treatment specifically targets the respiratory tract, which is compromised in COPD. The benefits of PMV decrease for the older patient, especially those aged over 85.

Abbreviations

CIR: cumulative incidence rate; COPD: chronic obstructive pulmonary disease; ICU: intensive care unit; LCA: latent class analysis; NHI: National Health Insurance; PMV: prolonged mechanical ventilation.

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Authors' contributions

M-CH was involved in the study design, data analysis, and manuscript preparation. H-ML was involved in sample storage and data analysis. LC was involved in the study design and manuscript revisions. F-CH was involved in the statistical analysis of the data and manuscript revisions. S-YC was involved in the statistical analysis of the data. Y-HY, P-SF, M-SL, L-CK and C-JY were involved in the study design and manuscript revisions. C-RC was involved in the overall study design and the preparation and revision of the manuscript. J-DW was involved in the overall study design and supervision, the data analysis, as well as the preparation and revision of the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Dynamic changes and lifetime scores of quality of life measured by WHOQOL-BREF for patients with different types of ischemic stroke

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Abstract

Background and Purpose: Few studies have estimated the dynamic changes and lifetime scores of quality of life measures (QOL) among patients with different types of ischemic stroke. The aim of this study was to quantify these changes to help understand and improve the clinical courses for these patients.

Methods: The hospital-based cohort, which consisted of 10,102 patients who experienced their first ischemic stroke during 1995-2007, was divided into four groups by stroke type: large artery atherosclerosis (LAA), lacunar stroke, cardioembolism, and other determined or undetermined etiologies. After linkage with the National Mortality Registry records of 1995-2007, our groups' survival functions were determined and extrapolated over a 600-month period, based on the ratio between the patient's survival rate and that of his/her age- and sex- matched reference groups at time t. These were estimated semi-parametrically through Monte Carlo simulations and hazard functions, with data taken from the vital statistics of Taiwan. The WHOQOL-BREF questionnaire was administered to a cross-sectional sample of 748 patients to estimate dynamic changes occurring at different times post-stroke. The survival functions were then multiplied across the different domains of QOL to obtain the lifetime scores for each domain for each ischemic stroke group. Multiple regression analyses were conducted to explore the effects of different risk factors on QOL, including major comorbidities and functional disabilities (as measured by modified Rankin scale).

Results: Patients with LAA seemed to be affected the most, in both terms of survival and quality of life. Their lifetime scores of QOL were 39.5 (SE = 2.7), 41.1 (2.8), 44.5 (2.9), and 48.10 (3.4) score-months in the physical, psychological, social, and environmental domains, respectively. Our multiple linear regression model found that lacunar stroke patients appeared to be affected the least in three domains of the WHOQOL, when compared with other types. When the models were adjusted for functional disabilities, the above differences in physical and social domain scores disappeared.

Conclusion: The dynamic changes in and lifetime scores of QOL were worst in patients who had incidence of LAA, indicating that demand for long-term care may be greater for patients with this type of ischemic stroke. Different levels of functional disability may explain the differences in physical domain scores.

Introduction

Each year approximately 5.7 million people worldwide die from stroke, making it the second-leading cause of global mortality.[1] Ischemic stroke is a highly heterogeneous disorder with different subtypes, each presenting with specific clinical aspects.[2-8] Quantifying the resulting disability and financial impact is not an easy task, especially in light of the aging population. Innovative technologies for preventing and treating strokes have significantly improved survival outcomes, but the dynamic fluctuations of quality of life at different times post-stroke, or "durations-to-date", seem less well documented. Financially, countries with national health care systems are often hit hardest, as the cost of care increases with survival time.[9] Many countries have adopted the Quality-Adjusted Life Year (QALY) as a measurement of cost-effectiveness.[10-12] However, methods using QALYs to determine utility-based economic policy cannot adequately address the detailed profile changes in quality of life for patients afflicted with different types of stroke. Instead, such dynamic changes must be evaluated using psychometric measurements to provide useful information for clinical decision-making.

The purpose of our study was to quantify these changes along the clinical courses for these stroke patients. Information concerning the specific prognosis of these ischemic stroke subtypes, including life expectancy, quality of life (QOL), risk factors of QOL, and score-time of QOL, could help improve clinical practice and rehabilitation treatments.[2-8] Based on the classifications of the Trial of Org 10172 in Acute Treatment (TOAST) system[13], we intend to explore health outcomes for different subtypes of stroke by associating survival functions with psychometric scores to obtain lifetime scores.[14-16]

Method

Establishing the ischemic stroke cohort

The study commenced after the approval of the Institutional Review Boards (IRBs) of the National Taiwan University Hospital (NTUH), and informed consent was obtained from every patient. We used data from the stroke registry at the NTUH[2, 3], which was established in 1995. At the time of this study, the registry contained information from 10,102 patients who had experienced their first ischemic stroke between 1995 and 2007. Diagnoses were made in accordance with key clinical features presenting in the following four subtypes: large artery atherosclerosis (LAA), lacunar stroke, cardioembolism, and other determined or undetermined etiologies.[3] Diagnostic criteria were adopted from the Trial of Org 10172 in Acute Treatment (TOAST) classification system.[13] Data collection was done during routine examinations, which included the use of brain imaging, echocardiography, ultrasonography of extracranial and/or intracranial arteries, and angiography, as previously described.[2,3] After comparison with stroke population records (registered under “catastrophic illnesses”) in the reimbursement data file of the National Health Insurance,[3] the study sample was demonstrated to be representative of the general Taiwanese population in terms of its sex, age, and stroke subtype distributions.

Survival analysis and extrapolation

Death certificates from the National Mortality Registry were also linked to patient records. Each patient was followed from the first day that s/he was diagnosed with ischemic stroke until either the date s/he became deceased or December 31, 2007, the study end date. The duration-to-date (i.e., the length of survival from the stroke episode to the date observed) is measured from time of diagnosis to either this study end date or patient death. We used the Kaplan-Meier method to estimate survival functions for the different subtypes of ischemic stroke. However, this method could only estimate the survival function up to the end of our follow-up,[14] while many young stroke patients in our cohort may survive longer than 20-30 years. Thus, we employed an extrapolation method we developed[15-16] that requires a simple assumption of constant hazard[17] and whose feasibility and accuracy have been demonstrated repeatedly in 17 different cancer cohorts.[18] Since stroke patients share the same likelihood of dying from cancer, traffic injuries, and other non-stroke illnesses as the general population, the cohort generally fulfills the constant excess hazard assumption, and we were thus able to extend the survival function to 50 years (600 months) post-diagnosis to accommodate our younger patients. In brief, the survival ratios between patients and age- and sex-matched referents were used to generate a linear extrapolation of a logit-transformed curve using the Monte Carlo method.[16] Detailed methods and mathematical proofs have been described in previous reports.[15-20]

Collection of quality of life data

All patients who visited the stroke clinic at the NTUH from February 2008 to June 2010 were invited to participate in the study. But only those who were able to independently understand and answer the questions on the WHOQOL-BREF via a direct face-to-face interview completed the questionnaires. Information from seven-hundred and forty-eight patients was collected and each gave informed consent. Each patient was interviewed once, with their quality of life assigned to a “duration-to-date,” measured from the date of first stroke diagnosis to the date of the interview.

We used a brief version of the World Health Organization’s Quality of Life survey (WHOQOL-BREF) to measure changes in quality of life.[21] The WHOQOL-BREF is an internationally-validated instrument designed to assess physical, psychological, social, and environmental domains that affect quality of life. This instrument was chosen because it is internationally recognized, validated for use in Taiwan, and free-of-charge.[21] Our survey included 26 original items plus two Taiwanese culture-specific items. Individual items are scored from 1 to 5 and summed up with similar items to obtain a domain score: *e.g.,* physical score. Each domain has the same range, from 4 to 20, and higher scores indicate a better quality of life. To employ iSQOL software (see below), we further transformed each raw domain score to a value between 0 and 1. Each raw domain score (DS) can be transformed using the formula: $\mathrm{Score}_{\mathrm{domain}} = (\mathrm{DS} - 4)/16$, for a scaled score from 0 to 1, where 0 represents death and 1 represents “perfect” health.

Estimation of dynamic changes and lifetime scores of QOL

Kernel-type smoothing using a moving average of the nearby 10% of values was performed to calculate the mean scores of each individual domain of the WHOQOL throughout the follow-up period: a maximum of 13 years.[14, 20] The survival functions were then multiplied with the QOL scores assessed by the WHOQOL-BREF for each different subtype of ischemic stroke in order to estimate their survival-adjusted health profile changes. The sum of the total area under this profile-change curve is each subtype’s lifetime score, as estimated by the following equation[14, 22]:

$$\text{Lifetime score of quality of life} = \int E[Qol(t \mid x)]\, S(t \mid x)\, dt + \eth\, [1 - S(t \mid x)]\, dt,$$

where $Qol(t \mid x)$ denotes the QOL function for condition x at time t and $S(t \mid x)$ represents the survival function for condition x at time t. Because we did not come across any patient who complained that his or her health condition was worse than being deceased, the second term of the above equation, denoting a health state worse than deceased, was set to zero. We used the software program iSQOL, built off of the *R* statistical software package, to calculate score time estimations and the 600-month extrapolations (free download at http://www.stat.sinica.edu.tw/jshwang).

Statistical analysis

The mean differences of QOL score among ischemic strokes were tested with a one-way analysis of variance (ANOVA) and Scheffe post hoc comparisons to detect significance. A Z-test was used to compare the life expectancies and lifetime scores of QOL of patients within subtypes. In addition to summarizing the data through descriptive statistical analysis, we conducted a multiple linear regression analysis. Domain scores were considered as the dependent variable with sex, age, education, duration-to-date, and comorbidities (including diabetes mellitus, coronary artery disease, carotid disease and cancer) as the covariates to be controlled. Patients classified in the lacunar stroke group were used as the reference population to explore the QOL changes of different subtypes of stroke. The model was further developed by adding the modified Rankin scale (mRS) to adjust for functional disability.[23]

Results

We recruited 748 patients who presented at the NTUH stroke clinic for observation after their first stroke. Patients with large artery atherosclerosis or lacunar stroke experienced the lowest life expectancy post-stroke, at 76.9 and 112.2 months, respectively (Table 1). Interestingly, patients classified in the cardioembolism group scored lowest on average on every QOL domain except environmental, even though they had the highest life expectancy post-stroke among the four subtypes (162.8 months). In contrast, patients classified in the lacunar stroke group scored highest on all four domains, even though patients of this subtype had the second lowest life expectancy, only behind LAA. None of the domain scores exceeded 14.5 on average, although patients seemed to enjoy the highest QOL in the environmental domain.

After controlling for different predictors in the multiple linear regression analysis, patients with LAA were found to score significantly worse than lacunar patients in the physical, social, and environmental domains (See Model A in Table 2). Compared with lacunar patients, those with other subtypes of stroke scored significantly lower in the physical and environmental domains as well. However, all effects on physical domains disappeared when the model was adjusted for functional disability: i.e., the mRS, which seems the most significant predictor of all domain scores (Model B in Table 2). Females seemed to score significantly better in the social domain, of which the regression coefficient remained stable even after adjusting for the mRS. Patients with higher education displayed higher QOL scaled scores across physical, psychological, and environmental domains.

Figure 1 shows the dynamic changes for all four-domain scores. Scores for the physical, psychological, and social domains in patients with cardioembolism began to go downhill three to five years after stroke onset, whereas those of patients with LAA appeared consistently low throughout all fourteen years of observation. After survival function adjustment, patients with LAA showed the lowest average lifetime QOL scores in all four domains over time, which were 39.5 (SE = 2.7), 41.1 (2.8), 44.5 (2.9), and 48.1 (3.4) score-months in the physical, psychological, social and environmental domains, respectively (Table 1 and Figure 2).

Discussion

To the best of our knowledge, this is the first study to quantify the dynamic changes and lifetime scores of QOL for patients with different subtypes of ischemic stroke based on TOAST criteria. The results showed that, after adjusting for confounding factors, the dynamic changes in QOL scores were the most negative in patients with LAA; the lifetime scores of these patients were also the lowest, followed by lacunar stroke patients, indicating a poor prognosis and probably a greater demand for long term care for patients with these subtypes.

Although the average life expectancy seemed to be highest for the cardioembolism subtype, this group only showed the highest domain score for environmental (Table 1). Furthermore, the scores of the other three domains appeared to deteriorate after three to five years (Figure 1). After controlling for demographic factors and comorbidities, the physical domain scores for LAA, cardioembolism, and “other” patients appeared the most affected (Model A in Table 2). However, all the differences in domain scores between subtypes disappear after the model is adjusted for functional disability: e.g., the modified Rankin scale (Model B in Table 2), indicating co-linearity between the major subtypes of ischemic stroke and functional disability. In other words, all strokes might be associated with additional neurological deficits, resulting from increased incidence of atherosclerosis, atrial fibrillation, left ventricular hypertrophy, and ischemic heart disease.[2, 4-5]

It is interesting that sex and education were significant determinants for WHOQOL scores in this study: the higher the education, the higher the score on each domain (except for social); this is corroborated by a previous study.[24] Since female gender was associated with a significantly higher score on social domain, future studies ought to explore methods for achieving gender equality in QOL outcomes. Similarly, Tang et al [7] reported that gender is an important factor for prognosis of QOL outcomes, particularly with regard to social functioning and role-emotional domains. In other studies[25-26], age was determined to be a predictor of unfavorable functional outcomes. However, our study did not replicate this tendency, after controlling for functional disability (i.e., with the mRS) and/or different stroke subtypes.

Our study has several limitations. First, for the lifetime extrapolation function of QOL, it was assumed that the patients would maintain their QOL at a similar level to that at the end of the follow-up period. Such an assumption could have resulted in an overestimation of QOL, because the actual QOL might gradually decline along with aging and increased comorbidities.[27-28] Second, although the demographic characteristics of our registry appeared to be similar to a random sample of the National Health Insurance, [3] our interviewed subjects were recruited from a single medical center. Thus, selection bias cannot be totally ruled out and generalization of our results must be conducted with caution. We recommend that future studies utilize subjects collected from a community hospital to corroborate this study’s results. Third, because the patients recruited for this study were only those able to independently understand and answer the WHOQOL questions, we may have overestimated the overall QOL scores by excluding patients with poor cognition or aphasia. But, actually these patients accounted for only two to three people. Finally, since surgical intervention data was not collected, this factor could be a potential confound. However, since surgery had not become a major treatment for stroke until the last several years, it only occupies a small proportion of patients; our adjustment for functional disabilities likely at least partially controls for such an issue.

Summary and Conclusions

This study has demonstrated that the dynamic changes in and lifetime scores of QOL can be quantified empirically to assist in clinical decision-making. After controlling for other risk factors, we found that QOL scores were worst in patients with LAA, likely due to poorer survival, implying a greater demand for long term care for patients in this ischemic stroke sub-population. When the model was adjusted to take functional disability among individual patients into account, differences in physical domain scores among different subtypes disappear, indicating an association between these two factors. Moreover, stroke patients with cardioembolism usually survive longer than those with other stroke subtypes, but their QOL might be affected three to five years after stroke onset. Future studies should also include subjects from a community hospital to corroborate this study's results.

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Table 1 Demographic characteristics, quality of life and lifetime score for patients with different subtypes of ischemic stroke hospitalized in the National Taiwan University Hospital (n=10,102), while 748 of them were measured with WHOQOL-BREF.

	Large artery atherosclerosis	Lacunar	Cardioembolism	Others
Number of subject	1,596	3,397	2,956	2,153
Sex (% female)	47.9	41.9	40.7	38.6
Age (mean ± SD)	68.5 (14.3)	67.4 (13.3)	67.0 (11.1)	65.5 (13.3)
Life expectancy (month)(SE) [*]	76.9 (4.8)	112.2 (3.6)	162.8 (9.2)	152.3 (6.7)
WHOQOL-BREF-interviewed cases	195	316	53	184
QOL of scores (mean± SD) †				
Physical	12.5 (2.5)	13.1 (2.3)	12.3 (2.6)	12.5 (2.5)
Psychological	12.6 (2.4)	13.0 (2.4)	12.3 (2.6)	12.6 (2.6)
Social	13.2 (2.6)	13.7 (2.6)	13.0 (2.5)	13.6 (2.5)
Environmental	14.0 (1.9)	14.5 (1.7)	14.1 (1.7)	14.1 (2.1)
Lifetime scores (months)				
Physical ‡	39.5 (2.7)	64.4 (1.8)	75.2 (8.1)	82.2 (5.0)
Psychological ‡	41.1 (2.8)	63.2 (1.9)	71.3 (8.2)	84.3 (4.5)
Social §	44.5 (2.9)	69.3 (2.2)	87.9 (5.7)	95.9 (6.7)
Environmental §	48.1 (3.3)	73.5 (2.1)	101.2 (7.2)	99.7 (6.7)

[*] Z-test: All pairs reached statistical significance (p<0.0084=0.05/6, a total of 6 paired comparisons)

† One-way analysis of variance (ANOVA): there was a significant difference in four groups, but Scheffe post hoc comparisons did not show any significant difference for all pairs.

‡ Z-test: there are significant differences (p<.0084) except for lacunar -cardioembolism pair, and cardioembolism -others pair

§Z-test: there are significant differences (p<.0084) except for cardioembolism- others pair

Table 2. Regression coefficients and standard error (in parentheses) resulted from multiple linear regression analysis of scores of WHOQOL-BREF and determinants in patients with different types of ischemic stroke

	Physical		Psychological		Social		Environmental	
	Model A*	Model B†	Model A*	Model B†	Model A*	Model B†	Model A*	Model B†
Ischemic stroke								
Lacunar	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Large artery atherosclerosis	-0.49 (0.24)‡				-0.49 (0.23)‡		-0.59 (0.18) §	-0.44 (0.17) ‡
Cardioembolism	-0.83 (0.35)‡						-0.52 (0.26) ‡	
Others	-0.59 (0.23)‡						-0.50 (0.17) §	-0.39 (0.16) ‡
Sex (female/male)					0.40 (0.17) ‡	0.41 (0.17) ‡		
Education (>12 years/≦12 years)	0.65 (0.17)§		0.64 (0.18) §	0.39 (0.17) ‡			0.43 (0.13) §	0.31 (0.12) ‡
Cancer							0.81 (0.35) ‡	
mRS		-1.18 (0.06)§		-0.80 (0.07) ‡		-0.45 (0.07) §		-0.38(0.05) §

[*] Model A was adjusted for age, duration-to-date, and comorbidities of diabetes mellitus, coronary artery disease, carotid disease and cancer

†Model B was adjusted for all the factors in model 1 plus mRS (modified Rankin scale)

‡P<0.05, §P<0.005