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The Value-Based Health Care:

a psychological perspective in cancer care

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List of Abbreviations

AIC: Akaike Information Criterion

AR1: First-Order Autoregressive

AS: Appetite Loss

BD: Bowel Dysfunction

BIP-Q: Brief Illness Perception Questionnaire

BMI: Body Mass Index

CBI-B: Cancer Behavior Inventory

CF: Cognitive Functioning

CFA: Confirmatory Factor Analysis

CFFM: Correlated Five-Factor Model

CFI: Comparative Fit Index

CO: Constipation

CS: Compound Symmetry

DI: Diarrhoea

DIF: Differential Item Functioning

DY: Dyspnoea

EBM: Evidence-Based Medicine

EF: Emotional Functioning

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30

EPIC: Expanded Prostate Cancer Index Composite

FA: Fatigue

FD: Financial Difficulties

GHS: Global Health Status

GMM: Growth Mixture Modeling

HD: Hormonal dysfunction.

HRQoL: Health-Related Quality of Life

HTA: Health Technology Assessment

ICCs: Intraclass Correlations Coefficient

ICHOM: International Consortium for Health Outcomes Measurement

IEO: European Institute of Oncology

IGCs: Individual Growth Curve

IN: Insomnia

IOM: Institute of Medicine

IPUs: Integrated Practice Units

LCGA: Latent Class Growth Analysis

LMR-LRT: Lo-Mendell-Rubin Likelihood Ratio Test

LOT-R: Life Orientation Test-Revised

MCFA: Multiple-group Confirmatory Factor Analysis

MI: Modification Index

MIMIC: Multiple Indicators-Multiple Causes

ML: Maximum Likelihood

MLR: Maximum Likelihood with Robust Standard Errors

NHS: National Health Service

NS: Nerve-Sparing

NSCLC: Non-Small-Cell Lung Cancer

NV: Nausea and Vomiting

PA: Pain

PC: Prostate cancer

PF: Physical Functioning

PROs: Patient-Reported Outcomes

QALY: Quality-Adjusted Life Year

QoL: Quality of Life

RARP: Robot-Assisted Radical Prostatectomy

RL: Role Functioning

RMSEA: Root Mean Square Error of Approximation

RSA: Resilience Scale for Adult

SB: Satorra-Bentler Chi Square

SD: Sexual dysfunction

SF: Social Functioning

SRMR: Standardized Root Mean Square Residual

TLI: Tucker-Lewis Index

VATS: Video-Assisted Thoracoscopic Surgery

VBHC: Value-Based Health Care

VBM: Value-Based Medicine

Figure Index

Abstract

This project has been developed in the breakthrough framework of the Value Based Health Care (VBHC), which aims at improving health outcomes at lower cost in different medical conditions. The VBHC paradigm has been applied in cancer care to improve the management of the disease, considering epidemiological, medical, psychological and economic outcomes.

Two studies have been designed and implemented to better investigate the psychological perspective of lung and prostate cancer patients, in the light of the VBHC paradigm.

The project identifies the trend of clinical and psychological status over time and predict this change with sociodemographic or medical variables. Several categories of patients characterized by different trends were identified, elucidating the psychological dimension of cancer patients.

A person-oriented approach was used to analyze patients' recovery. One-year Quality of Life (QoL) trends in early stage of lung and prostate cancer patients undergoing surgery were identified. Patients' recovery after surgery was characterized by both an overall decrease of symptoms and an increase of health and functioning over time.

Prostate cancer patients showed different longitudinal trajectories of urinary incontinence and sexual dysfunction. In lung cancer patients, pre-surgery QoL, type of surgery, perioperative complications, and age, affected the post-surgery QoL as well as the linear and quadratic trends over time.

Through the implementation of this holistic approach, the predictive model of patients' recovery will be developed, thus improving medical decision-making, the choice of treatment, and patients' awareness about their care process. Potential harms, QoL, and expected outcomes will be more predictable and better manageable. Participants will be more empowered, being more aware of their post-surgical care.

1. Introduction

1.1 The meaning of value in health care

The concept of value is a prominent topical issue in health care. Individual needs, preferences, and ethics affected the meaning of value, which in turn has been influenced by different cultures or historical periods [1]. The necessity of finding better ways of redirecting the incentives away from volume and toward value has led patients, physicians, policy makers, and other stakeholders to focus their attention on the meaning of value and its main features [2]. Even if a unanimous consensus on value's definition has not yet been achieved, it is commonly accepted that values in health care may be defined as normative guidelines to evaluate actions or conditions and to influence the decision-making process [3–5]. Reputable organizations and associations based their definitions of value on expert judgment and empirical studies correlating value's characteristics with measurable outcomes. The American Heart Association (AHA) underlines that, even though clinical efficacy and outcomes constitute the primary basis of good medical practice, value plays – together with costs – an important role including positive results in patient's outcome, safety, and satisfaction [6].

Different studies pointed out that the value's definition changed with the reference sample: doctors' values, most of the time, do not match the values of the patients, and vice versa [3,6,7]. In 2008, the Institute of Medicine (IOM) held a 2-day workshop to explore key stakeholders' perspectives on the value in health care, seeking to understand the meaning of value [7]. Patients, providers, economists, payers, and employers, claimed that a mutually acceptable agreement among different points of views was difficult to be reached. Providers considered value on the appropriateness of care and on the effectiveness of evidence-based interventions, while economic representatives defined value as the clinical benefit achieved for the money spent. Patients, however, focused their attention on the ability of health care to satisfy their goals: a valuable intervention is a way of treating that also fulfills their needs [8]. Patient's needs are frequently measured taking into account different aspects related to

Quality of Life (QoL), such as pain, emotional and cognitive functioning, or functional impairment [9,10]. Moreover, a recent review [11] on patient's perceptions of quality of care emphasizes how communication, healthcare access, and shared decision-making are the key elements in a valuable healthcare environment.

The absence of a common and widely accepted meaning of value allows each movement in healthcare practice to take into account different components of value. Over the last 10 years, the value was the key theoretical concept of different healthcare paradigms, leading to birth of different models of care.

1.2 The Value-Based Health Care (VBHC): an in-depth explanation of the paradigm

Between 2006 and 2013 at the Institute for Strategy and Competitiveness, based at the Harvard Business School, M.L. Porter and E. Teisberg (2006) developed and proposed a new health care model based on value, "a breakthrough framework for redefining healthcare competition based on patient value"[12].

A Value-Based Health Care (VBHC) should refer to three important principles [13]. Firstly, the proper goal for every stakeholder should be better health for their patients, not more treatments. Improving access to poor care or containing costs should be replaced with the overarching goal of enhancing patients' value, defined as the best "*health outcomes achieved per dollar spent*" [14]. The health outcomes refer to the patient's outcomes achieved over the full care cycle, the actual results of the care in terms of how well the patient actually does. Costs are the total costs of care for the patient's condition, the actual cost of providing care and the resources involved in delivering care. Therefore, increasing value for patients means increasing quality, that is improving health outcomes without escalating costs or lowering costs without compromising outcomes[15]. Secondly, treatment delivery should be based on medical conditions and on the course of treatment a patient has to undergo. Each stakeholder plays a prominent role in determining the appropriate patient's care pathway and the overall result derives from the quality of the total set of services provided. Lastly, outcomes should be measurable and recorded[13,16]. Data must be collected along the entire

patient cycle of care because the outcomes *achieved* are more effective measures than the number of services *delivered* - that would not be possible to previously know if they were properly and successfully used. Moreover, the outcomes should be interpreted on the basis of the costs effectively delivered across the full care cycle: cost reduction without considering outcomes would be dangerous and self-defeating[13].

1.2.1 The Value Agenda

These principles are the basis for a value transformation grounded on patients' needs, health outcomes achieved, and costs collected in health-delivery organizations that follow the full care cycle of specific medical conditions. Porter and colleagues (2006) defined this strategy the "Value Agenda"[12,15].

This strategic agenda has six interdependent and mutually reinforcing components: if they were advanced together, the implementation of a new model of health delivery would be easiest and fastest (see Fig.1).
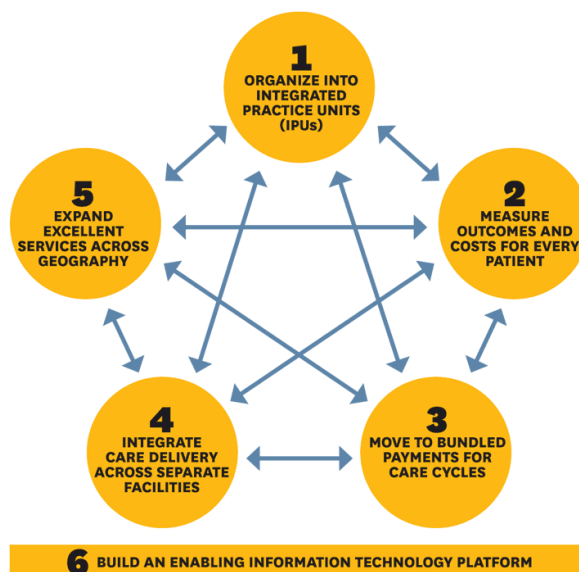
Figure 1: The Value Agenda. The model has been taken by Porter and Lee (2013)

This model replaces the fragmented health care system with the introduction of Integrated Practice Units (IPUs) where each medical condition or set of related conditions are dealt by a multidisciplinary team of clinical and nonclinical providers trained to provide both patient and inpatient care. The current system is organized around the services provided, around the doctors, the tools. This agenda focuses on organizing care around the patient's problem and

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needs. Each medical condition is an interrelated set of patient medical circumstances and possible complications that frequently co-occur and involve multiple specialties and services (patient education, engagement, and follow-up). Uncoordinated, sequential visits to multiple providers and different departments would be converted into integrated and high-quality care within the same organization. The IPUs do not only refer to a clinical condition but also include programs for patient education, engagement, and follow-ups. Physical health IPUs should include dedicated mental health providers who understand the mental health needs of the patients they treat, detect developing mental illness, and intervene early. Incorporating mental health clinicians into primary care will improve patient value. Outpatient, inpatient, and rehabilitative care, as well as supporting services (e.g. nutrition, social work, behavioral health), would be encompassed in the full cycle of care[15].

Health outcomes and costs for every patient should be recorded continuously in line with the care. Outcomes should cover the full cycle of care for the condition and track the patient's health status after care is completed. The measured outcomes can be arrayed in a three-tiered hierarchy: health status achieved, the process of recovery, and sustainability of health (see Fig.2). Each tier includes two broad levels with various outcomes dimensions of patient's health, each of them measured at different timing by several metrics. The patient health status (Tier 1) includes survival (or mortality) and the recovery achieved (clinical and functional status). The process of recovery (Tier 2) is composed of time required to achieve recovery over the care cycle (e.g. a phase of diagnosis, treatments, follow-up) and the disutility of the care process. This last dimension includes missed diagnosis, failed treatment, discomfort, ability to work or function normally while undergoing treatment, short-term complications, retreatment, and errors, together with their consequences. Lastly, Tier 3 includes the sustainability of health outcomes achieved referring to the degree of health maintained, possible disease recurrences and long-term complications, or to new health problems related to the previous treatments[17]. The selection of the outcome's measures should be determined on each medical condition and patient's initial status, sometimes also termed risk

factor for its probability to adjust patients' recovery. A different set of outcomes are defined and combined all together accordingly to specific diseases: patient initial indicators (such as type of disease, age,…), acute care outcomes, complications or co-occurring conditions form the overall result of the full cycle of care. To define which type of measures should be appropriate for a specific disease, providers should understand the most relevant health circumstances and the set of services affecting patient's results, the near- and long-term consequences of care, and the risk factors that may adjust the patient's condition[17].
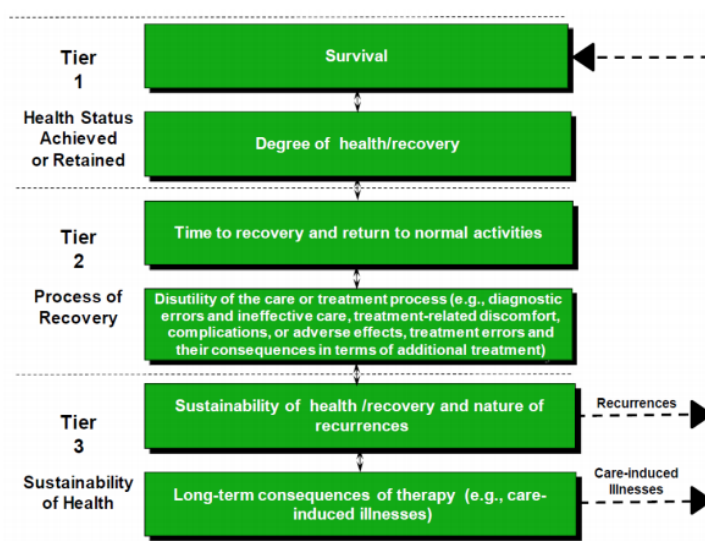
Figure 2: The Outcomes Measures Hierarchy. The schema has been taken by Porter 2010, What is value in health care

Moreover, stakeholders have to record the total of expenses in treating the full medical condition: the resources implied in patient's care should be combined with the cost of supplying each of them, such as the personnel, instruments, and administration facilities.

The third point of this overarching strategy for a value transformation includes a new type of payment approach: a value-based health care system should adopt a bundled payment to cover the full cycle of care for each type of disease (acute, chronic or preventive condition), a whole bundle of services required to deal with the patient's medical problem. The bundled payment refers to the entire episode of care: a lump sum for the continuum of care associated with a specific medical condition is taken to a provider group, instead of paying separately for each performance provided (fee-for-service payment). In this type of payment, providers should primarily think about the entire patient experience among all care settings and

between episodic visits, and then convey them in a total cost of care encompassing all spending for the patient (see Fig. 3)[18].
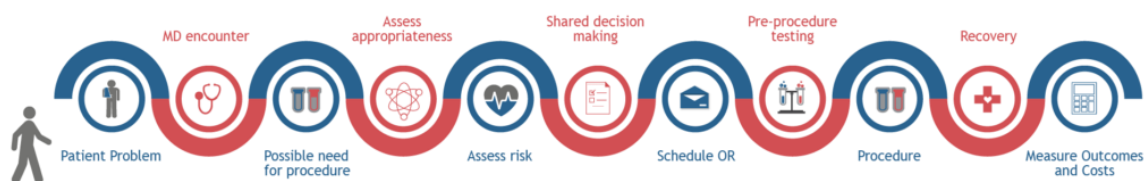
Figure 3: The Bundled Payment. The figure has been taken by Value-Based Care, Bundled Payments, & Direct Contracting, Shearwater Health, 2019.

Therefore, bundled payment means setting a single price for each medical condition, including all visits and exams required for good care. It is not the cost of individual service, but the total cost of all the services required to deal with a specific medical problem. To maximize value for the patient, a bundled payment should 1) cover the entire care cycle required to treat a condition, 2) mandatorily report outcomes, such as returning to normal function, reducing pain or complications, 3) be adjusted for risk (e.g. sociodemographic characteristics or living conditions) that may affect patient's health condition, 4) provide a fair profit by adding a margin over the full costs for an effective care, and 5) include a "stop-loss" provision to limit providers' exposure to unusually high costs from catastrophic or outlier cases.

The fourth point of the Value Agenda is to integrate care delivery across separate facilities in order to eliminate the fragmentation and duplication of care. To optimize the types of care delivered in each location, an integrated care delivery system requires the definition of the aim of services provided and the concentration of volume of similar treatments in fewer locations according to the medical condition and its acuity level, the costs and intensity of resources and the need for convenience[15].

This integration would be further achieved by the application of the fifth step of this strategic agenda: the expansion of services across locations. Health care delivery systems should

extend their reach through the strategic expansion of excellent IPUs following a hub-and-spoke or a clinical affiliation model. A hub-and-spoke model implies the presence of both a single IPU (hub) giving initial clinical consultations and establishing new treatment plans, and different satellite facilities (spokes) delivering less complicated - but more cost-effective - care. In most of the cases, fixed staff members are supported by several clinicians who rotate among locations. On the other hand, the clinical affiliation model is based on the affiliation of each IPU with community providers: leading providers use rural and community hospitals partners to deliver care rather than adding capacity to the single IPU. Through these models, both IPUs and local facilities will increase their value: the former could broad its regional reach, share management fees, revenue, or complex cases; while community providers could benefit from the expertise, experience, and reputation of the parent IPU and often improve their market.

To implement all these steps, it is crucial to have an Information Technology platform able to help providers in integrating care across the care cycle, to better connect different facilities and IPU across geography or patients to the process. This platform should be patient-centered, with an understandable and standardized terminology, and all data (e.g. physician notes, images, chemotherapy orders, lab tests) stored in a unique virtual place accessible to all parties involved in the patient's health care. To respect these characteristics, the system should be designed in a simple way to extract information, including templates and expert systems for each medical condition[15].

These interrelated and organizational imperatives drive the health care system towards a paradigmatic shift from a volume-based to value-based care. The Value Agenda is set up to organize care around what patients need and to move away from a health care system based on what physicians do towards a patient-centered system.

1.3 Applying the Value-Based Health Care system

The aging population and increasing incidence of chronic diseases, innovative technologies, and new powerful drugs, led to a cost increase. The best way to reduce expenses is to define

and measure the health outcomes around the medical condition and improve them in order to add value to the healthcare path. Therefore, the aim of the VBHC model is to improve health outcomes at lower cost in different medical condition, from preventive to chronic situations. The organization, management, and measurement of outcomes and process of clinical care cycles constitute the core elements for a value transformation in hospitals and facilities. Along with process measurement, the outcomes should include performance-improvement goals of providers and patients' indicators of high-quality care[17,19]. The attention toward the health care system shifts from a volume of activity approach to a value-based system, focused on results concretely obtained: doctors and hospitals would be paid based on outcomes achieved, not on numbers of procedures done, patients treated, or how much they were charged[14]. Moreover, rather than charging a patient for each individual test or service, payments would be bundled, supporting cost-effective care delivery while still being compliant with evidence-based guidelines. Primary care units should be replaced by care delivery processes based on subgroups of patients with similar needs, focusing on similarities in the type of care required and not on discrete diseases type such as diabetes, hypertension, or depression[20]. Electronic medical records for each patient would eliminate repetitive and unnecessary tests and procedures. To treat patients in a more efficiently and less time-consuming way, healthcare practitioners would communicate through the help of care coordinators. Patients would move through this integrated system more quickly and ideally would have fewer readmissions and less frequent hospitalizations or trips to the emergency room[20,21].

Changing the healthcare system is a long challenge partially carried out with the implementation of some of the concepts described above within the value-based framework. Nevertheless, the alignment of countries' current health systems to key components of the VBHC model is still in progress. In 2016, the Economist Intelligence Unit (EIU) conducted a study on the adoption of value-based healthcare principles in 25 countries all over the World: 17 qualitative indicators, grouped into four domains, were identified to describe

different aspects of the VBHC model [22]. "Enabling context for value in healthcare", "Measuring outcomes and costs", "Integrated and patient-focused care", and "Outcome-based payment approach" were the identified four areas to display the level (from "Low" to "Very high") of each country's alignment with the value-based healthcare concepts. The United States, UK, and Sweden obtained the best scores, followed by Canada, France, and Australia. In fact, these countries were scored from "Very High" to "Moderate" in all the proposed domains. Germany and Japan showed "Low" scores only in the "Integrated and patient-focused care" and in "Outcome-based payment approach" area, respectively. The remaining nations were scored with "Low" in more than one area. Italy was not included in the study [22].

The diversity among healthcare systems worldwide may lead to different time to implement the VBHC principles among countries, while differences in organizational processes and disease types may lead hospitals of each country to face great challenges in shifting towards value-based models.

1.3.1 The VBHC system in Europe

Globally, healthcare systems are plagued by a combination of rising costs, reduced access to good medical care, and a lack of transparency and coordination in assisting the delivery of effective treatment. Porter and Teisberg argue that the value was not based on enhancing long-term patient outcomes, but on short-term cost-saving cycles which focused on the clinical absence of disease[12]. Lack of standardization in measuring enhanced long-term patient outcomes has contributed to limited transparency in comparative treatment performance and the spread of non-evidence-based treatment-related information and practices[12]. The health care systems in Europe are still based on a supply-driven model rather than a patient-centered model, focusing on cost-containment rather than on patients' value[23].

Several European countries have been trying to implement the VBHC paradigm in accordance with the healthcare systems. Nevertheless, the lack of consensus about what

performance indicators should be used, who to reward and how to quantify the value of incentives to motivate further efficiency, has slowed down the adoption of VBHC and reduced the collection of cost and outcomes in the area of ambulatory and primary-care-based interventions. Up to now, Germany, Spain, France, Portugal, UK, and Italy have been trying to apply some aspects of the paradigm[24]. Below a brief overview of these countries' attempts to implement the VBHC paradigm in their healthcare systems.

Germany focused on improving the process of delivering care, rather than on measuring patient outcomes and experiences. Increasing minimal volumes for procedures and creating centralized healthcare units (Integrated Practice Unit) specialized in specific diseases or procedures are the most common attempts to improve quality in Germany. Pay for performance and giving the regions greater power to take charge of healthcare policy are other implemented strategies to improve the healthcare system. In recent decades, data collection gained in importance: the Martini-Klinik became the leading hospital in showing that a better data collection focused on the patient experience may improve the overall outcomes[25]. The Cologne Care Research and Development Network (CoRe-Net) developed other three German projects based on the value-based framework. The Core-Net supported studies on patients' and caregivers' trajectories with heart disease and mental comorbidity, palliative care, and all organizations caring for the patient (inpatient and outpatient care, rehabilitation and private practitioners). Through a mixed-method design these research projects collected quantitative and qualitative data, analyzing medical, psychological variables and questionnaires on healthcare and statutory insurance funds[26–28].

In Spain, the continuous improvement in health technology assessment and the decentralization of the health administration enabled the sharing of best practices and the flexibility for innovation in regions. Using an online survey, the International Consortium for Health Outcomes Measurement (ICHOM) collected data on Spanish, Dutch and English patients with chronic kidney disease to establish a set of standardized health outcomes and

enable their measurement in routine clinical practice[29]. On the other hand, Parra and colleagues (2017)[30] applied the value-based paradigm at five hemodialysis centers, collecting clinical and economic outcomes. The obtained results helped stakeholders and policy makers in creating better context for healthcare and decision-making improvement.

France and Portugal focused on the building of new Health Technology Assessment (HTA) and the implementation of primary healthcare and integrated care delivery, but both healthcare systems are still in progress. In Portugal, the high impact on the budget of some medical diseases, such as obesity, chronic renal disease, and pulmonary hypertension, has led to a faster implementation of integrated disease management programs and the development of coordinated medical and nursing services in hospitals, primary healthcare, and long-term care. On the other hand, France has also introduced new cost-effectiveness measures and financial incentives to encourage the creation of multi-disciplinary teams and the use of bundled payment systems[31,32].

England has implemented more "value-based" changes in its healthcare system than other European countries. The National Health Service (NHS) is different from its "European neighbours": it is more centralized, is funded by general taxation, including national insurance contributions, and is both publicly financed and operated primarily through the public sector, although market reforms have steadily introduced private providers within England over the last few decades. It has already adopted pay-for-performance models and has expertise in technology assessment for more than a decade[33]. The Quality and Outcomes Framework, the Best Practice Tariffs, and the Commissioning for Quality and Innovation are different English pay-for-performance programs providing financial incentives for primary or secondary care of chronic diseases[34]. Even if no single health system has yet to realize all aspects of the value agenda, England endorsed the concept of value as outcomes per cost, the adoption of IPU and the integration of primary and secondary care across the whole patient pathway to deliver value[35].

The Italian healthcare system is decentralized at both national and regional level: the significant degree of regional autonomy may lead to a lack of consistency and transparency in the provided healthcare services or a responsibilities' overlap. The subsequent problems of miscommunication between the centers and the regions may get to a potential waste of efforts and costs. On the other hand, the development of a health technology assessment (HTA) infrastructure to collect, analyze and share data has been a slower process[36]. In 2006, the Italian Health Technology Assessment Network (SIHTA) was founded to include all the separate HTA units among academic medical centers, research hospitals, and regional and local health authorities. Nevertheless, the multi-level structure of HTA in Italy has not yet provided full co-ordination and harmonization of practices and outcomes across the country. Moreover, just five out of Italy's 21 regions and autonomous Provinces - Veneto, Emilia-Romagna, Lombardy, Piedmont, and Tuscany – have established structures to include HTA in their healthcare decision-making process. Nevertheless, there is a significant degree of variation in the way these regions have developed HTA. Many single bodies play a role in HTA decision-making in Veneto, for example, while the other four regions have a more centralized structure for carrying out the evaluation process. The industry is involved in the process only in Emilia-Romagna, while patient involvement occurs only in Piedmont; the other three regions provide no role for either industry or patients[37]. Many of the regions with the most developed HTA systems are also better organized and more efficient, with the result that they attract patients from other regions as well. Regional programs are nonetheless frequently constrained by a lack of sufficient data, which undermines transparency[36].

Along with the individual attempts to implement some aspects of the VBHC paradigm in each European country, in 2009, in Netherlands, a groups of academic and healthcare professionals founded the Value-Based Health Care Center Europe which brings national and international experiences together, and is right on top of the implementation of Value-Based Health Care[38]. This European Network aims to facilitate the implementation of the concepts of VBHC, by developing new and existing methodologies, creating best practices,

and disseminating these among the international network. According to these principles, from 2014 this organization made up the VBHC Prize in order to recognize inspiring initiatives that focus on patients, engage patients and their families while delivering excellent patient value[38].

1.3.2 The VBHC system in cancer care

Nowadays, the VBHC delivery initiative has been adopted in medical acute conditions or in chronic and primary care. The former includes joint replacements, different type of cancer, cardiological and neurological diseases, urological and gynecological procedures, and the observations room patients after Emergency Department care. On the other hand, primary care and chronic conditions focused on diabetes, heart failure, dementia, degenerative neurological diseases, and psychiatric disorders[39]. Several American and European hospitals, following the VBHC paradigm, have implemented some of its components, while others are still in development. In fact, care delivery is frequently fragmented, requiring multiple departments and disconnected providers to organize patient's process of care. Implementing dedicated facilities staffed by dedicated teams and integrating different clinical interventions for a specific disease in a single care pathway may provide better care to patients and reduce the recovery burden, positively affecting the other measured outcomes[16].

As reported by the World Health Organization Report (2016), cancer causes the second greatest burden on patients across the European Union[40]. Today, the global cancer burden has risen to 18.1 million cases and 9.6 million cancer deaths [41], compared to five years ago, when the Global Cancer Statistics (GLOBOCAN, 2012) stated: "an estimated 14.1 million new cancer cases and 8.2 million cancer deaths occurred in 2012 worldwide"[42]. In 2018, the European Union carries a significant load of the global cancer burden with almost one-quarter of the estimated cancer cases occurring in this area[41]. Following Porter's idea, Johansen and Saunders (2017)[43] analyzed the healthcare organizations adopting the VBHC paradigm. Starting from these observations, they developed some

guidelines to apply the theoretical paradigm in cancer care. The four main steps to transition current cancer care into a value-based system are 1) defined for each type of cancer universal Patient-Reported Outcomes (PROs) over the full care cycle, 2) constitute multidisciplinary cancer-specific units, 3) establish a system capturing all data provided, and 4) continually improve treatment strategies through research. Thus, the VBHC has been applied to analyze specific cancer types and improve the management, combining epidemiological, medical, psychological and economical outcomes. Mapping the entire care cycle for a specific disease allows the stakeholders to identify all relevant outcomes and their measurement[14]. Fig. 4 shows the value chain of care delivery in breast cancer.

	MONITORING/ PREVENTING	DIAGNOSING	PREPARING	INTERVENING	RECOVERING/ REHABING	MONITORING/ MANAGING
INFORMING AND ENGAGING	• Advice on self screening • Consultations on risk factors	• Counseling patient and family on the diagnostic process and the diagnosis	• Explaining patient treatment options/ shared decision making • Patient and family psychological counseling	• Counseling on the treatment process • Education on managing side effects and avoiding complications • Achieving compliance	• Counseling on rehabilitation options, process • Achieving compliance • Psychological counseling	• Counseling on long term risk management • Achieving compliance
MEASURING	• Self exams • Mammograms	• Mammograms • Ultrasound • MRI • Labs (CBC, etc.) • Biopsy • BRACA 1, 2… • CT • Bone Scans	• Labs	• Procedure-specific measurements	• Range of movement • Side effects measurement	• MRI, CT • Recurring mammograms (every six months for the first 3 years)
ACCESSING THE PATIENT	• Office visits • Mammography unit • Lab visits	• Office visits • Lab visits • High risk clinic visits	• Office visits • Hospital visits • Lab visits	• Hospital stays • Visits to outpatient radiation or chemo-therapy units • Pharmacy visits	• Office visits • Rehabilitation facility visits • Pharmacy visits	• Office visits • Lab visits • Mammographic labs and imaging center visits
	• Medical history • Control of risk factors (obesity, high fat diet) • Genetic screening • Clinical exams • Monitoring for lumps	• Medical history • Determining the specific nature of the disease (mammograms, pathology, biopsy results) • Genetic evaluation • Labs	• Choosing a treatment plan • Surgery prep (anesthetic risk assessment, EKG) • Plastic or onco-plastic surgery evaluation • Neo-adjuvant chemotherapy	• Surgery (breast preservation or mastectomy, oncoplastic alternative) • Adjuvant therapies (hormonal medication, radiation, and/or chemotherapy)	• In-hospital and outpatient wound healing • Treatment of side effects (e.g. skin damage, cardiac complications, nausea, lymphedema and chronic fatigue) • Physical therapy	• Periodic mammography • Other imaging • Follow-up clinical exams • Treatment for any continued or later onset side effects or complications

Figure 4: The Care Delivery Value Chain in breast cancer. The table has been taken by Porter 2010, What is value in health care.

Therefore, the outcomes measures hierarchy in breast cancer implicates the collection of specific data for each tier. As suggested by Porter and colleagues, Tier 1 (survival and degree of recovery) includes survival rate, degree of remission, functional status, breast conservation, and depression. Tier 2 (time to recovery and disutility of care) would focus on the time of remission and functional status, infections, nausea, suspension of therapy, failed therapies, limitation of motion, depression. Finally, Tier 3 (stability of recovery and long-

term consequences) may measure cancer recurrence, sustainability of functional status, incidence of secondary cancers, brachial plexopathy, fertility/pregnancy complications, and premature osteoporosis. Moreover, risk factors and initial conditions should be considered to make a baseline risk adjustment and consider their influence on all levels of the outcome hierarchy. Risk factors for patients with breast cancer may be the stage of disease, type of cancer, receptor status (positive or negative), sites of metastases, previous treatments, age, menopausal status, general health, including co-morbidities, and psychological and social factors. A great number of American and European healthcare organizations started collecting clinical data, but none of them measured the entire outcome hierarchy for the medical conditions[14]. The Martini-Klinik, an important German hospital, measured cancer patients' functional and oncological outcomes following surgery. Patients were invited to complete a questionnaire on their quality of life, urinary and sexual functioning at four different times: 1) prior to their surgery, 2) one week after surgery, 3) three months after surgery, and 4) one year after surgery[25]. In 2012, the International Consortium for Health Outcomes Measurement (ICHOM) started to create standard sets of outcomes for specific medical conditions. Nowadays, breast, prostate, colorectal, and lung cancers have specific lists of standardized outcomes, measurement tools, and time points and risk adjustment factors[44]. The outcome measurement provides better opportunities for understanding whether care is benefitting patients and which treatments are most effective for each medical condition. Moreover, these data may allow a greater understanding of expenditures and foster a cost review: seven Dutch hospitals (the *Santeon* Network) highlighted an increase of 74% in the rate of reoperation due to complications in breast cancer patients and a reduction of nearly 30% in unnecessary inpatient stays. This network implemented the value-based healthcare concepts among three different cancer patient's groups (breast, prostate and lung) following the subsequent steps: 1) introduce a multidisciplinary team to define measured outcomes, 2) acquire internally clinical knowledge to better manage the care cycle and validate new medical processes, 3) share externally the knowledge to accelerate

improvements, and 4) collaborate with patients and payers to move toward value-based contracting[45].

Several web-based platforms and mobile information technologies have been implemented to collect PROs and define the trajectories of patients' recovery. Different hospitals in the US developed PRO measurement programs: the Memorial Sloan Kettering Cancer Center and the Group Health Cooperative in Seattle adopted IT platforms to collect outcomes in routine outpatients cancer care[46,47]. In 2016, a German hospital established a digital system to measure the PROs of breast cancer patients by the Breast ICHOM dataset and collected over 2500 questionnaires of 541 subjects[48]. The scientific literature shows that the installation of eHealth systems would increase data collection, reduce data loss and minimize errors in the data entry process. Moreover, patients declared that they would felt more comfortable using electronic systems, in comparison to paper and pencil-based methods[43,49]. The measurement of both clinical and patient-oriented health outcomes would be easier if specialty-oriented departments became cancer-specific multidisciplinary practice units which provide the full care cycle, thus favouring the financial transition from a fee-for-service to a bundled-payment system[43,46]. Nowadays, the IPUs are frequently implemented in hospitals treating a specific disease. The American MD Anderson Cancer Center applied the value-based principles organizing and integrating care within various medical fields and adopting a bundled payment program which divided expenses into three episodes of care (pre-treatment, treatment, and post-treatment phases)[50,51]. The Erasmus MC's implemented the value-based strategy on breast cancer patients: an IPU with a multidisciplinary team of stakeholders was created collected and analyzed outcomes by electronic health records[52].

Several attempts have been made to apply the VBHC paradigm in European and American organizations: different healthcare systems imply different possibilities to make some changes in the care process and, most of the times, great changes require several years to be adopted. At this moment, the VBHC offers a new way of managing the healthcare process

and a possibility to discriminate which patients' group better benefit from an intervention, enhance patient empowerment, and ensure that limited resources are used for the greatest patient benefit[43].

2. Empirical contribution

2.1 The VBHC paradigm at the European Institute of Oncology

According to different healthcare systems and national governments, some aspects of the VBHC paradigm have been implemented around Europe.

A literature search was conducted on Pubmed, Web of Science, Cochrane Library, Medline Ovid, Embase and Scopus using various combinations of database-specific controlled vocabulary (subject headings), supplemented by keywords, title and abstract terms for the concepts and synonyms relating to Value-Based Health Care (VBHC) in Italy. The aim of this review was to investigate if some Italian hospitals have already applied the VBHC to medical practice. The search strategy was included in the *Appendix 1*.

Accruing evidence obtained by literature investigation reported that only two healthcare hospitals - located in Lombardy and Veneto regions - are applying and implementing only some principles of the VBHC model. The Veneto Region, through the VBHC working group, is currently developing a pilot project in the field of cardiology and cardiac surgery, including in the study cohort patients who underwent transcatheter aortic valve implantation (TAVI)[53]. On the other hand, the European Institute of Oncology (IEO, Milan) has been collecting patient's health outcomes and the related direct/indirect costs to increase health benefits and save costs.

In 2015, IEO applied the VBHC model in different oncological divisions, starting the Value-Based Medicine (VBM) project. Following Porter's idea, the primary aim of the project was to build an equation that relates altogether clinical outcomes (efficacy and tolerability of treatment, complications) with direct and indirect costs incurred by the system. The result of this equation is the value, intended as a measure of different dimensions of health that represents the maximum health protection achieved for each euro spent. Therefore, the term "value" was not due to the "cost" of an intervention, but rather to the overall assessment of patient's benefits and complications, integrating all these aspects in one macro - indicator.

The holistic approach of the VBHC paradigm implies the collection of economic, medical and psychological outcomes, that will contribute to design personalized predictive model of patient's recovery after surgery. Through this predictive model of care, participants would be more empowered, receive a more complete framework of post-surgical care pathway, and improve their health literacy and decision-making.

Starting from these premises, the project would analyze principal and interaction effects between outcomes and costs investigating the associations among psychological, medical and economic aspects of patient's process of care, and studying if the psychological status may impact on costs, rehabilitation, and drug consumption or medical examinations.

The study has been conducted on patients with prostate and lung cancer. The VBM project will be also conducted on breast cancer patients.

Since the VBM project is a multidisciplinary study, several stakeholders have simultaneously carried out research studies investigating different aspects of the care process. Social workers and economists collected and analyzed economic outcomes, physicians and trained nurses focused on the medical condition over time, and psychologists investigated patient's well-being. All the researchers followed the VBHC principles and shared their results to build a unified predictive and personalized model of care.

Data were collected at different time points consistently with the patient's recovery and follow ups. At pre-surgery (baseline), the project was personally explained to each subject and only after the informative consent they were enrolled in the study. The baseline recruitment was vis-à-vis, while the other time points of data collection were conducted by telephone or e-mail. Clinical and psychological information were extracted from medical records and standardized questionnaires, while social workers collected economic data following a search grid.

2.2 Introduction to the research studies

Within the VBM project, in collaboration with the Psychoncology Division, two pivotal researches have been designed and implemented on lung and prostate cancer patients. In

order to involve the psychological outcomes in the VBHC paradigm, the following aims have been developed:

1. To identify the trend of clinical and psychological status over time and predict this change with sociodemographic or medical variables;

2. To identify categories of patients characterized by a different trend of clinical and psychological status over time and assess differences in sociodemographic or medical variables among them;

3. To further investigate the psychological dimension of cancer patients.

The studies on prostate and lung cancer patients are already completed, while the Breast Cancer Unit has been starting the recruitment. Therefore, the obtained results on prostate and lung cancers will be here discussed.

The VBHC paradigm theorizes QoL as the only psychological factor that may affect the patient's value. For this reason, our studies on prostate and lung cancer patients focused on QoL measurement. Sub-chapters 2.3, 2.4, 2.5, and 2.6 will include the validation studies of the used QoL questionnaires and the predictive trajectories of patients' recovery after surgery both from a clinical and psychological perspective. Since the included studies had different sample, statistical analyses and results, the Discussions will directly follow each Results section. The statistical analyses conducted on prostate cancer patients were able to satisfy both the first and the second of the primary aims. On the other hand, the sample of lung cancer patients was too small to identify categories of patients characterized by different trend of clinical and psychological status over time (second aim). Due to this statistical limitation, we only identify the overall trend of clinical and psychological status over time and predict this change with sociodemographic or medical variables.

To sum up, paragraphs 2.3 (study 1a) and 2.4 (study 1b) will show the Italian validation of the questionnaire (the EPIC-26) used to measure QoL in prostate cancer patients and their trends over the care process, respectively. On the other hand, paragraphs 2.5 (study 2a) and 2.6 (study 2b) will include the EORTC QLQ-C30 Italian validation (used to collect data on

QoL of lung cancer patients) and the identified trajectories of QoL subdimensions over one-year after surgery.

2.3 Study 1a: Validation of the Italian Version of the Abbreviated Expanded Prostate Cancer Index Composite (EPIC-26) in Men with Prostate Cancer

A recent systematic review showed that, among the great availability of prostate-cancer specific questionnaires measuring PROs, the Expanded Prostate Cancer Index Composite (EPIC) is the most suitable cancer-specific survey in urology departments to measure patient's physical and psychological well-being[54]. Through the "Evaluating Measures of Patient-Reported Outcomes" (EMPRO) tool, the EPIC obtained, along with the University of California Los Angeles-Prostate Cancer Index (UCLA-PCI), the highest score in terms of concepts and population intended to assess, and very high scores in validity, interpretability, and responsiveness. Moreover, EPIC was also recommended because it is the only questionnaire investigating hormonal and irritative/incontinence urinary dysfunction domains. The original version of EPIC is composed of 50 items and is developed by Wei and colleagues[55]. Considering the difficulty of administering the questionnaire during clinical practice, a short version was introduced composed of 26 items. The new version, named EPIC-26 (*Appendix 2*), is the most used brief self-report scale and it has already been validated in Norway, USA, China and Germany[56–59].

Its administration allows physical and psychological information to be collected on specific dimensions, as urinary incontinence, urinary irritation, bowel, sexual and hormonal dysfunction, scored from 0 (worst) to 4 or 5 (best). All domains of EPIC-26 are highly correlated with all domains of the longer version EPIC-50 ($r \geq 0.96$)[56–59].

The proposed factor structure for the EPIC-26 is a correlated five-factor model (CFFM) [59,60]. As shown in Figure 5, urinary incontinence and urinary irritation are both measured by four items; bowel and sexual dysfunctions are both measured by six items, while five items measure hormonal dysfunction. A single item (i.e., item 9) measuring overall urinary

symptomatology is a stand-alone item and is not included in any of the domains because it overlaps on both urinary incontinence and urinary irritation.

High internal consistency and test-retest reliability - Cronbach's alpha ≥ 0.70 and $r \geq 0.69$ respectively - have been reported in all the domains[59–61]. These psychometric properties, along with being less time-consuming and easier to use than the full version, encouraged the use of the EPIC-26 in clinical and research settings over time.

Considering the pivotal role of the EPIC-26 to assess QoL in prostate cancer patients[54], the main aim of this study was to develop an Italian version of this self-report measure and to evaluate its psychometric properties in term of dimensionality, longitudinal invariance, and reliability in term of both internal consistency and test-retest reliability.
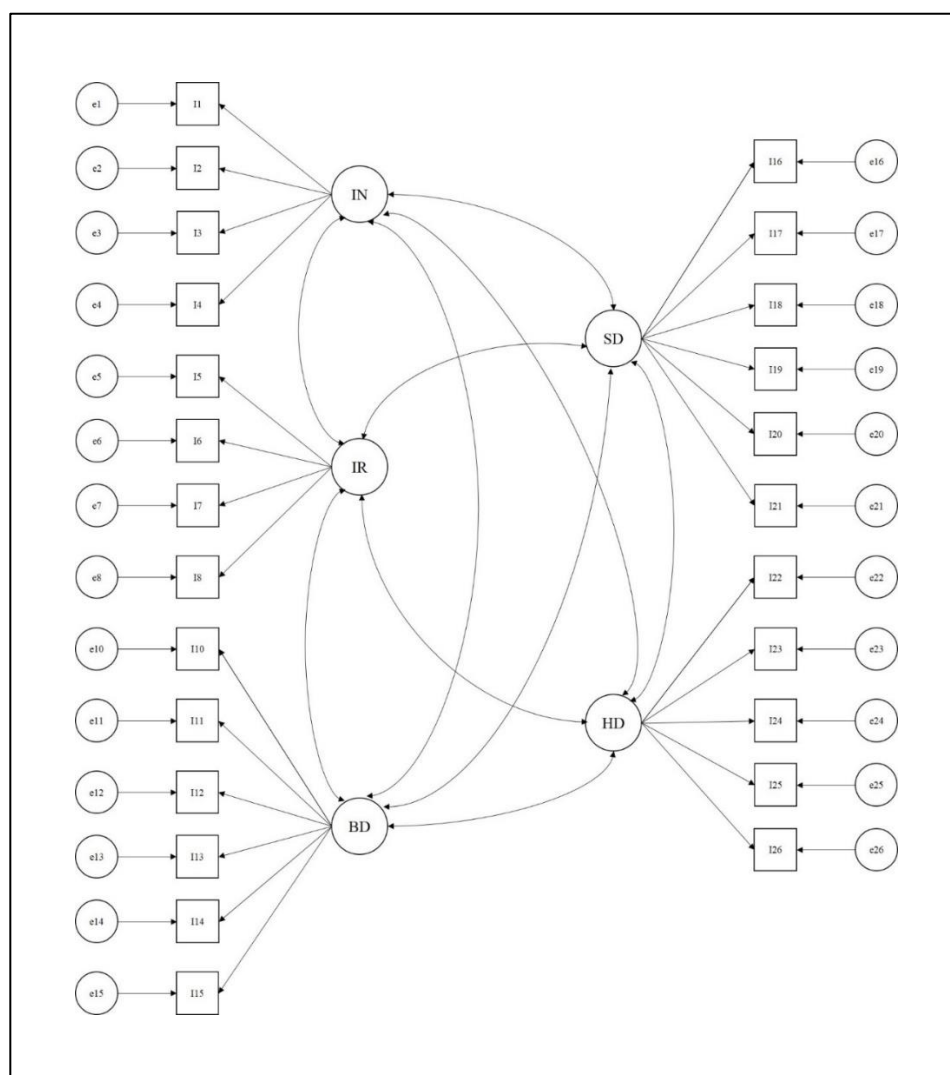
Figure 5: The correlated five-factor model

Note: IN = Urinary incontinence; IR = Urinary irritation; BD = Bowel dysfunction; SD = Sexual dysfunction; HD = Hormonal dysfunction.

2.3.1 Materials and method

Participants and procedure

An Italian sample of 284 patients with localized prostate cancer who had undergone Robot-Assisted Radical Prostatectomy (RARP) was recruited at the European Institute of Oncology in Milan between July 2015 and July 2016. Patients were included in the study if they: 1) were diagnosed with localized prostate cancer, 2) were native Italian speakers, 3) referred to the Value-Based Project and 4) had neither neurological nor psychopathological problems. They completed the questionnaire 45 days (T1) and 6 months (T2) after RARP surgery. Informed consent was provided and signed by each participant. The participation in the study was voluntary and at each moment, patients could withdraw their consent. The study was developed in accordance with the principles stated in the Declaration of Helsinki (59th WMA General Assembly, Seoul, 2008) and was approved by the Ethical Committee of the European Institute of Oncology.

Language equivalence

Transcultural adaptation of the EPIC-26 survey in Italian was done using forward and backward translation by two experts[62]. One English native speaker translated the original English EPIC-26 version into Italian. Then, two expert psychologists assessed the consistency of the translation and approved the first version of the Italian EPIC-26. This version was pretested in a cognitive debriefing study with ten prostate cancer patients in order to assess its readability, understand ability, and comprehensibility. The cognitive debriefing was conducted by a psychologist. The time taken by each patient to complete the EPIC-26 was recorded. Patients then completed a cognitive debriefing task in which they asked about the clarity of the instructions and items, and the level of ease of response to each item.

Instructions ($M = 4.80$, ds $= 0.632$) and items ($M = 4.96$, ds $= 0.08$) were rated as clear on a five-point Likert scale (ranging from $1 =$ not at all to $5 =$ completely). Items were also rated as easy to complete ($M = 4.96$, ds $= 0.07$) on a five-point Likert scale (from $1 =$ not at all to

5 = completely). Only two patients asked for further information about the "13.b" item ("breast tenderness/enlargement"): they did not understand the meaning of the question and asked for more information. They did not know this side effect and were not able to visualize it as a possible consequence of the disease. Then, a second mother tongue speaker translated this version back into the English language. The results of this back-translation were virtually identical to the original English version.

Statistical Analysis

The psychometric properties were assessed using structural equation modeling in a sample of patients who had undergone Robot-Assisted Radical Prostatectomy (RARP). Specifically, we aimed at assessing the goodness of fit of the CFFM for the EPIC-26 using confirmatory factor analysis (CFA) and testing reliability. Then, longitudinal invariance was assessed to evaluate the ability of the EPIC-26 to reliably and validly measure its relevant constructs over time. Longitudinal invariance is a necessary requisite to assess stability and change of constructs over time since without invariance it is not possible to distinguish between true changes in outcomes over time and differences in the psychometric properties of the instrument.CFA with robust maximum likelihood (MLR)[63] was performed with Mplus 8.2 to evaluate the CFFM of the EPIC-26 separately at T1 and T2. Overall goodness-of-fit of the proposed models was evaluated assessing multiple indices of fit: the chi-square test ($X2$), the root mean square error of approximation (RMSEA), the comparative fit index (CFI), the Tucker-Lewis index (TLI), and the standardized root mean square residual (SRMR). The model fit was firstly evaluated using the $X2$ statistic. However, because of its sensitivity to the sample size, other indices were also used[64]. Specifically, values above .90 for the CFI and TLI, a RMSEA below .06, and a SRMR below .08 indicate a good fitting model. The assessment of longitudinal invariance is a sequential process with seven specific steps. As reported in Table 1, configural, metric, scalar, and residual variances invariances were sequentially performed and followed by invariance of the latent factor variances, covariances, and means. The main assumption of configural invariance is that the same

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factor structure will hold in the two waves. Metric and scalar invariance respectively assume that factor loadings and item intercepts are equivalent across time. The assumption of residual invariance is that the residual variances of items are equivalent across time. Equality of residual variances implies equal reliability over time. Finally, the invariance of factor variances, covariances, and means assume respectively that latent factor variances, invariances, and means are equal across the two waves. The difference in CFI (i.e., ΔCFI) between a model and the subsequent level of invariance was considered to evaluate whether the hypothesis of invariance should be retained. Measurement invariance is indicated by a ΔCFI less than or equal to -.010[65]. When invariance was not found, we tested partial invariance by checking modification index (MI). At each step, we identified all the non-invariant parameters by reviewing MI and then freely estimated these parameters across time. Analyses were performed using the full-information maximum likelihood estimator, which allows for inclusion of cases with partially missing data.

Table 1 – The sequential process to assess longitudinal invariance.

Model	Title	Description
A	Configural model	The factor structure is the same across waves
B	Metric model	A + all factor loadings are constrained to be equivalent across waves
C	Scalar model	B + all item intercepts are constrained to be equivalent across waves
D	Residual variances model	C + all residual variances of items are constrained to be equivalent across waves
E	Factor variances model	D + all latent factor variances are constrained to be equivalent across waves
F	Factor covariances model	E + all covariances among latent factors are constrained to be equivalent across waves
G	Factor means model	F + all latent factor means are constrained to be equivalent across waves

Internal consistency was assessed by computing respectively Cronbach's alpha of each dimension in the two waves. Test-retest reliability was computed by considering intraclass

correlations (ICCs). Specifically, ICCs (and their 95% confidence interval) were used to examine correlations between repeated measurements of each QoL dimensions obtained from the same patient at different times (i.e., T1 and T2). We used ICC Model 3 (i.e., two-way mixed effects, absolute agreement, single measure/rater) to quantify test-retest reliability[66,67]. ICC values below 0.50 were considered to indicate poor reliability, from 0.50 to 0.75 moderate, from 0.75 to 0.90 good, and above 0.90 excellent reliability[68].

2.3.2 Results

As shown in Table 2, participants had a median age of 63.4 ± 7.12 and a BMI of 26.6 ± 3.54. Two hundred and thirty-three men underwent radical prostatectomy with nerve-sparing (NS) surgical procedure (N=159 with bilateral NS; N=75 with unilateral NS), while the other 17.6% (50/284) of the sample undergone surgery without NS. The distribution of item responses was reported in Table 3.

Table 2 - Sample characteristics

	N
Age	63.4 ± 7.12
BMI	26.6 ± 3.54
Type of surgery	
Bilateral NS	159
Unilateral NS	75
Without NS	50

Table 3 – The distribution of item responses

ITEMS	T1		T2	
	M	SD	M	SD
1	2,13	1,59	3,72	1,62
2	2,75	0,76	3,30	0,68
3	1,41	1,08	0,46	0,73
4a	1,92	1,26	0,90	1,07
4b	0,62	0,94	0,10	0,38
4c	0,20	0,58	0,01	0,13
4d	0,79	1,09	0,40	0,77
4e	1,90	1,21	1,08	1,14
6a	0,42	0,79	0,28	0,63
6b	0,34	0,72	0,21	0,59
6c	0,03	0,19	0,03	0,26
6d	0,02	0,12	0,03	0,19
6e	0,75	1,00	0,28	0,62
7	1,55	0,90	1,31	0,69

8a	1,58	0,94	1,82	1,08
8b	1,87	1,19	2,28	1,27
9	1,91	1,13	2,19	1,20
10	1,91	1,33	2,15	1,36
11	1,57	0,97	1,73	1,07
12	2,81	1,39	3,02	1,46
13a	1,12	0,47	1,25	0,73
13b	1,08	0,38	1,10	0,40
13c	1,56	0,91	1,56	0,99
13d	1,90	1,08	1,54	0,94
13e	1,38	0,78	1,34	0,80

At T1, the CFFM model displayed a good fit to data [SB X2 (265) = 553.092, p = .000; RMSEA = .055; CFI = .921; TLI = .911; SRMR = .067]. Similarly, the model showed an adequate fit also at T2 [SB X2 (265) = 605.020, p = .000; RMSEA = .060; CFI = .907; TLI = .894; SRMR = .061]. Specifically, all standardized factor loadings except the ones for items 13 and 23 are significant at T1. At T2, all standardized factor loadings are significant except the ones for items 7, 12, and 13.

Table 4 summarizes the sequential process of assessing measurement invariance by reporting fit indices of each model and the ΔCFI between them. In the first step, configural invariance was assessed. Specifically, fit indices attested that the CFFM had a good fit in both waves hold in the two waves [SB X2 (1105) = 1892.249, p = .000; RMSEA = .044; CFI = .913; TLI = .904; SRMR = .062]. Equivalence of the factor loading across waves was then examined in the metric invariance model. This model did not fit significantly worse than the configural model (ΔCFI = -.010) thus indicating that each item was related to the latent factor equivalently across waves. The scalar invariance model fitted significantly worse than the metric invariance one (ΔCFI = -.028). Subsequently, the MIs suggested that the intercept of items 14, 5, 25, 6 and 21 were the main sources of significant misfit and should be freely estimated across waves. After doing this, the partial scalar invariance model did not fit significantly worse than the metric invariance one (ΔCFI = -.009) and thus denoting that T1 and T2 had the same expected response for each item except for items 14, 5, 25, 6, and 21 at the same absolute level of the traits being measured. The residual variances invariance

model fitted significantly worse than the partial scalar one (ΔCFI = -.012). The MIs suggested that the residual variances of items 13 and 22 should be freely estimated across the two waves. After doing so, the partial residual variances invariance model did not significantly fit worse than the previous invariance model (ΔCFI = -.005) and thus denoting that the amount of item variance not accounted by the latent factor was the same across the two waves except for items 13 and 22. After reaching partial measurement invariance, structural invariance was assessed by evaluating factor variances, factor covariances, and factor means invariance. The factor variance model did not fit significantly worse than the partial residual variances invariance model (ΔCFI = -.002) thus indicating equivalent variances or namely equal amounts of individual differences in QoL across the two waves. Results demonstrated the equivalence of relationships among the five latent factors across waves as indicated by a no significant decrease of model fit between the factor covariances invariance model and the previous model (ΔCFI = -.004). Finally, the factor means invariance model fitted significantly worse than the factor covariances model (ΔCFI = -.036). The MIs suggested that the means of the latent factors of urinary incontinence and urinary irritation should be freely estimated across the two waves. After doing so, the partial factor means invariance model did not significantly fit worse than the previous invariance model (ΔCFI = -.006) and thus denoting that only these two factors means were significantly different and decreasing over time.

Table 4 – Results of the sequential process of assessing measurement invariance of the EPIC-26.

Model	SB X^2	df	p	RMSEA	CFI	TLI	SRMR	ΔCFI
Configural Invariance	**1892.249**	**1105**	**.000**	**.044**	**.913**	**.904**	**.062**	**-**
Metric Invariance	**2003.830**	**1125**	**.000**	**.047**	**.903**	**.895**	**.068**	**-.010**
Scalar Invariance	2279.990	1145	.000	.052	.875	.866	.071	-.028
Partial Scalar Invariance - Item 14	2225.603	1144	.000	.051	.881	.872	.071	-.022
Partial Scalar Invariance – Item 5	2196.445	1143	.000	.051	.884	.876	.070	-.019
Partial Scalar Invariance – Item 25	2155.922	1142	.000	.050	.888	.880	.070	-.015
Partial Scalar Invariance – Item 6	2126.187	1141	.000	.049	.891	.883	.069	-.012
Partial Scalar Invariance – Item 21	**2101.490**	**1140**	**.000**	**.048**	**.894**	**.886**	**.069**	**-.009**

Residual Variance Invariance	2232.515	1160	.000	.051	.882	.875	.078	-.012
Partial Residual Variance Invariance – Item 13	2219.857	1159	.000	.050	.883	.876	.075	-.011
Partial Residual Variance Invariance – Item 22	**2167.399**	**1158**	**.000**	**.049**	**.889**	**.882**	**.072**	**-.005**
Factor Variance Invariance	**2191.584**	**1163**	**.000**	**.050**	**.887**	**.881**	**.077**	**-.002**
Factor Covariance Invariance	**2231.046**	**1173**	**.000**	**.050**	**.883**	**.878**	**.078**	**-.004**
Factor Mean Invariance	2562.749	1178	.000	.057	.847	.841	.098	-.036
Partial Factor Mean Invariance – Urinary Incontinence	2383.217	1177	.000	.053	.867	.862	.081	-.016
Partial Factor Mean Invariance – Urinary Irritation	**2291.617**	**1176**	**.000**	**.051**	**.877**	**.872**	**.078**	**-.006**

Note: SB = Satorra-Bentler Chi Square; df = degree of freedom; RMSEA = Root mean square error of approximation; CFI = Comparative fit index; TLI = Tucker-Lewis index (TLI); SRMR = Standardized root mean square residual; ΔCFI = Difference in CFI between models.

This final model showed an adequate fit to data [SB X^2 (1176) = 2291.617, p = .000; RMSEA = .051; CFI = .877; TLI = .872; SRMR = .078]. Standardized parameters of this model are reported in Figure 6. All the standardized factor loadings are significant and above .30 in absolute value with the exception of items 5, 6, 12, 13, 22, and 23. Intercepts of items 5, 6, 14, and 25 decreased across waves while the intercept of item 21 increase from T1 to T2. Regarding residual variances, all non-equivalent items showed a decrease of residual variance except for items 13 and 22 that showed an increase of residual variance over time. All the factor variances and covariances are equivalent across time attesting the structural stability of the EPIC-26 questionnaire. Factor correlation ranged between .187 and .622 in absolute value with the highest link between urinary incontinence and urinary irritation. Finally, three-factor means (i.e., bowel, sexual, and hormonal dysfunctions) showed to be equivalent across waves; on the contrary, urinary incontinence and urinary irritation decrease from the first to the second wave.
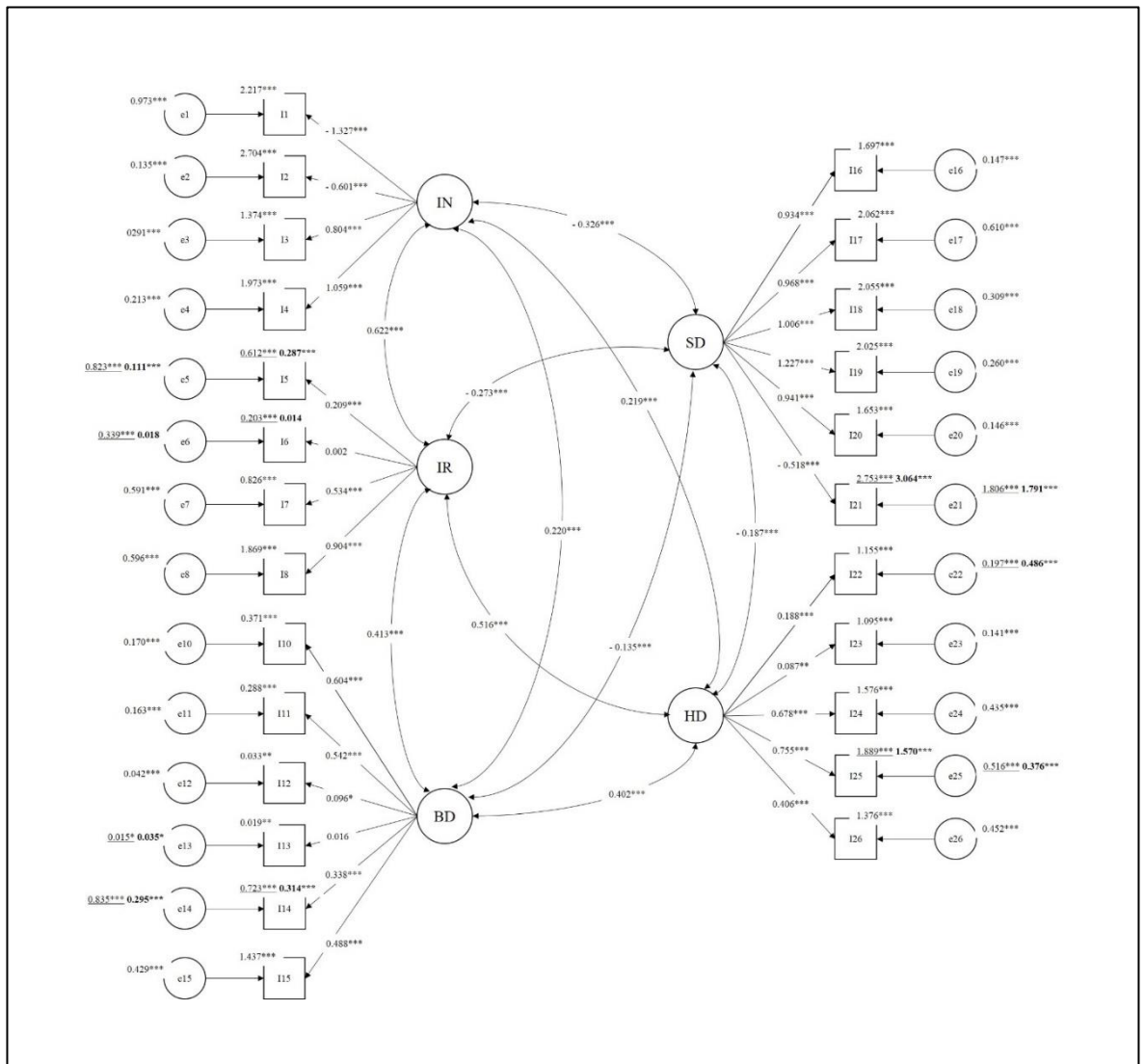
Figure 6: Standardized parameters of the final CFFM.

Note: IN = Urinary incontinence; IR = Urinary irritation; BD = Bowel dysfunction; SD = Sexual dysfunction; HD = Hormonal dysfunction.

Results of the reliability analysis attested the good internal consistency and test-retest reliability of each dimension (Table 5). Specifically, all Cronbach's alphas could be classified as minimally acceptable (i.e., above .65) except for low Cronbach's alpha for hormonal dysfunction at T1 and urinary irritation at both waves. Urinary incontinence and sexual dysfunction display optimal reliability with values of Cronbach's alpha above .80 in both waves. Finally, ICCs attested the good test-retest reliability of each dimension. Specifically, ICC for urinary incontinence could be classified as good, whereas the ICCs for the remaining dimensions could be considered as moderate.

Table 5 – Cronbach's alphas and ICC assessing internal consistency and test-retest reliability of the EPIC-26.

Dimension	T1 Cronbach'alpha	T2 Cronbach'alpha	ICC correlation (95% CI)
Urinary incontinence	.886	.862	.764 (.717-.804)
Urinary irritation	.585	.518	.600 (.529-.662)
Bowel dysfunction	.699	.736	.536 (.458-.606)
Sexual dysfunction	.860	.902	.552 (-.088-830)
Hormonal dysfunction	.638	.700	.636 (.570-693)

2.3.3 Discussion

This study represents the first attempt to assess the validity of the Italian version of the EPIC-26. The factor structure, longitudinal invariance, and reliability of the Italian version of the EPIC-26 were investigated in a sample of Italian prostate cancer patients who had undergone RARP. Results of the CFA demonstrated that the proposed CFFM provided a good fit to data at both waves in these patients. These results support the usefulness and validity of computing separate scores for each of the five domains of urinary incontinence, urinary irritation, bowel dysfunction, sexual dysfunction, and hormonal dysfunction. The results of the reliability analyses attest the acceptable internal consistency and test-retest reliability of most of the EPIC-26 domains. The urinary irritation subscale is the only dimension showing a poor internal consistency with values of Cronbach's alpha below the minimally acceptable cut-off at both waves. This result is consistent with previous empirical evidence regarding the weak reliability of this subscale in the Chinese version of the EPIC-26[58]. Following suggestions by Lam and colleagues[58], the low reliability of this subscale may be determined by the high proportion of patients reporting no problem on the first two items (pain on urination and bleeding with urination) of this domain and a higher proportion of patients reporting moderate problems or incomplete emptying and need to urinate frequently during the day. Another possible explanation of this low reliability is the limited number of

items in this domain compared with other domains (urinary incontinence, sexual, bowel, and hormonal dysfunction). Notably, the first two items measuring urinary irritation, alongside with item 2 (urinary control), item 13 (bloody stools), item 22 (hot flashes), and item 23 (breast tenderness) display a low factor loading below .30. Thus, all these items could be considered weak indicators of their respective dimensions. Further research is needed to identify more reliable indicators of urinary irritation in patients with prostate cancer by developing new ad-hoc items. Regarding test-retest reliability, all dimensions displayed at least moderate reliability.

Testing longitudinal measurement invariance is a pre-requisite for understanding whether changes in patients' urinary incontinence, urinary irritation, bowel dysfunction, sexual symptomatology, and hormonal dysfunction over time reflect true changes in quality of life or rather changes in the psychometric properties or structure of the EPIC-26 over time. This study also demonstrated the good longitudinal invariance of the EPIC-26. This self-report measure was administered to the same sample of patients with prostate cancer who had undergone RARP in order to assess all the sequential steps of measurement invariance over time. Results demonstrated a full weak invariance of the EPIC-26 across time. Specifically, its entire factor loading is invariant over time and, thus, indicating that all of them are related to their respective domains equivalently across waves. We also demonstrated a partial strong invariance and a partial strict invariance of the EPIC-26 over time attesting respectively that the majority of the expected responses are equivalent over time and that the amount of item variance not accounted by the latent factor was the same across the two waves. The non-invariant thresholds of items 5, 6, 14, 21, and 25 suggested that patients evaluate these specific symptoms differently over time. Specifically, responses to these items revealed that patients who had undergone RARP reported a significant decrease over time of pain or burning on urination, bleeding on urination, bloody stools, and lack of energy. Conversely, they showed a significant increase in amount of problem-related to their sexual function or the lack of sexual function.

Finally, after the partial strict invariance, results also attested the structural invariance of the EPIC-26 across the two waves. We found the equivalence of factor variances and covariances over time suggesting respectively that the same amounts of individual differences in patients' quality of life were found between T1 and T2 and that strong structural stability exists among the five EPIC-26 domains over time. Moreover, the five EPIC-26 domains showed from moderate to strong stability across time. Finally, the results of the factor mean invariance demonstrated that the levels of bowel, sexual, and hormonal dysfunctions tend to be equal over time. On the other hand, self-reported levels of urinary incontinence and irritation significantly decreased from 45 days to 6 months after the RARP. A large number of studies using this instrument (the 50- and 26-item versions)[54] and the high number of language translations[56–59,69–74] make an Italian validation necessary. The Italian validation of the Expanded Prostate Cancer Index Composite – Short Form confirms its validity and reliability in measuring Quality of Life in prostate cancer patients over time. Beyond its reliability, the Short Form is easier than the longer version of the questionnaire, reducing administration burden with only 10 minutes for the compilation[54].

Limitations

One of the main limitations of this study is the lack of other self-report measures of quality of life or patients' well-being, which could be useful to better assess convergent and/or divergent validity of the EPIC-26. However, we did not include any other measures to minimize the burden on such patients.

Moreover, the EPIC-26 was administered to patients who had undergone RARP only; the lack of other treatment types may affect the internal consistency. More precisely, our results may show poor internal consistency in the urinary irritation subscale because patients who had undergone RARP did not suffer from this side effect.

2.4 Study 1b: Predicting trajectories of recovery in prostate cancer patients undergone Robot-Assisted Radical Prostatectomy (RARP)

Despite all advancements in surgical and radiant treatments, a recent study shows that regardless any treatments, 90% of PC survivors reported at least one physical impairment during the two-years post-diagnosis. Sexual, urinary and bowel dysfunctions are the most common functional consequences after PC treatments and they may persist for several years[75,76]. Compared to radiotherapy and active surveillance, men who underwent robot-assisted radical prostatectomy (RARP) reported greater negative side effects especially in the first 6 months from the surgery, even though there was a partial recovery[77]. Sixty percent of men suffer from urinary incontinence and sexual problems after surgery, that are often related to distress and fatigue symptoms. Following a variable-oriented approach, several studies investigate the trend of these symptoms showing that patients live longer with these side effects that deeply affect their quality of life for months after treatment[78–82]. Nevertheless, it would be also important to identify different categories of PC patients with different trends in recovery over time through a person-oriented approach that can better display which kind of patients may have higher difficulties in the recovery of their functional and psychological abilities. The person-oriented approach is a valid alternative to the traditional variable-oriented methodology. The main analytic units of the variable-oriented approach in health research are individual behaviours, health-related variables or construct that may vary both within populations or over time[83]. In this kind of approach inter-individual differences are rarely taken into account because they are considered random and negligible [84]. On the contrary, the main assumption of the person-oriented approach is that people are unique and that this uniqueness is measurable and worth knowing[85]. The main analytic units of this approach are individuals or homogeneous subpopulations. From this perspective, inter-individual differences are meaningful and may be especially helpful to classify individuals into distinct classes. Individuals belonging to the same class are similar to each other while they are quite different from those classified in other classes. Concerning

prostate cancer, Chambers et al. (2017)[86] applied a person-oriented approach to understand which factors can affect different trajectories of patients' recovery in Quality of Life, life satisfaction and psychological adjustment after different prostate cancer treatments, but nobody has already focused the study research on physical function's recovery in men with prostate cancer after RARP surgery.

Clinical and sociodemographic characteristics may foreshadow the partial recovery of men treated with RARP. Different studies showed that age, body mass index (BMI), and diabetes may predict long-term post-operative incontinence after RARP[87,88]. While preservation of the neurovascular bundle, age, and pre-surgery sexual condition were considered as positive predictors of potency recovery following RARP[89–91]. Therefore, patients' characteristics play an important role in months after surgery: some pre-intervention sociodemographic and clinical variables may influence and predict the typical trend of patient's recovery after robot-assisted radical prostatectomy.

Physical dysfunctions are normally present during the months after surgery, highly affecting patient's survivorship and Quality of Life[79]. This new study perspective may help people involved in the care process to better identify possible trajectories of physical and psychological outcomes and predict which of the identified categories of patients would have greater difficulties in their recovery.

The aim of this research study is to identify one-year trends of patients' urinary and sexual dysfunctions from a clinical and psychological point of view and understand whether sociodemographic (i.e., age) and medical variables (i.e., diabetes, BMI, nerve sparing, pre-surgery scores of urinary incontinence and sexual dysfunction) could differentiate among patients following these different one-year longitudinal trajectories.

2.4.1 Materials and Method

Participants and Procedure

An Italian sample of 478 men with localized PC who participated in the Value-Based Project and undergone RARP was enrolled at the European Institute of Oncology in Milan between

July 2015 and July 2016. Patients were included in the study if they: 1) were diagnosed with localized PC, 2) were native Italian speakers, 3) referred to the Value-Based Project and 4) had no neurological or psychopathological problems. All eligible men were firstly asked to give written informed consent and then were asked to complete the self-report EPIC-26 survey. At the pre-intervention, sociodemographic and clinical characteristics were also collected, in particular age, BMI, presence or not of diabetes, PSA Class, Charlson Comorbidity Index, Gleason Score, ASA Class, and preservation or not of the neurovascular bundle (nerve-sparing procedure). Clinical characteristics were described in Table 6. They completed the EPIC-26 questionnaire at the pre-hospitalization (T0), 45 days (T1) and 3 (T2), 6 (T3), 9 (T4), and 12 months (T5) after RARP surgery. Since our aim was to study the trend of sexual and urinary dysfunction after surgery and we saw that there was low outcomes variability among patients before surgery, we excluded the baseline outcomes and run the analyses starting from T1, that is 45 days after prostatectomy. Baseline outcomes (i.e., urinary incontinence and sexual dysfunction), alongside with sociodemographic and other clinical variables, were used to predict patients' membership in the identified longitudinal trajectories of urinary incontinence and sexual dysfunction over time. All information and data were collected and analyzed by a multidisciplinary team of the Value-Based Project. The Ethical Committee of the European Institute of Oncology approved the study.

Table 6. Sample clinical characteristics

	Sample (%)
Pre-surgery variables	
Gleason Score	
≤ 6	46.1
7	39.4
8	10.7
9-10	3.8
PSA Class	
Less than 4	12.8
4-10	66.9
More than 10	20.3
ASA Class	
1	18.7

2-3	81.3
BMI Class	
Normal (< 27)	66.7
Overweight (≥27)	33.3
Charlson Index	
<1	72.8
≥1	27.2
Surgery variables	
Nerve Sparing	
No	26.4
Unilateral	55.9
Bilateral	17.7
Post-surgery variables	
Complications	
No	89.3
Yes	10.7

Measures

The Expanded Prostate Cancer Index Composite - Short Form EPIC-26 is the most used cancer-specific survey in Urology divisions to measure patient's well-being[59,92,93]. The EPIC-26 is a brief self-report scale, collecting medical and psychological information on urinary incontinence, urinary irritation, bowel, sexual and hormonal dysfunction with a Likert-scale from 0 to 4 (or 5 in some items). Urinary Incontinence subscale consists of 4 items investigating leaking urine, urinary control, number of pads used per day and overall urinary functioning, in the last 4 weeks. Sexual dysfunction includes items on the ability to have an erection, ability to reach an orgasm, quality of erections, frequency of erections, and overall sexual function, in the last 4 weeks. Higher scores in subscales indicate the worst medical conditions or higher problem perception. The EPIC-26 was administered at the pre-hospitalization (T0), 45 days (T1) and 3 (T2), 6 (T3), 9 (T4), and 12 months (T5) after RARP surgery.

Age and BMI were collected for each participant at the pre-hospitalization. According to the WHO Guidelines[94], a BMI cut-off of 27 divided the sample into two classes: patients with a BMI< 27 were included in the "normal weight" class, while those with a BMI≥27 were included in the "overweight" class.

Diabetes and the preservation of the neurovascular bundle were included in medical variables. Three classes were identified: 1) patients undergone to radical prostatectomy with bilateral nerve sparing procedure, 2) patients undergone to radical prostatectomy with unilateral nerve sparing, and 3) patients undergone to radical prostatectomy with no nerve sparing.

Statistical Analysis

To identify different longitudinal trajectories of patients with PC undergone RARP based on their initial status and change over time in urinary incontinence and sexual dysfunction, we performed a Latent Class Growth Analysis (LCGA) conducted separately for each of these two EPIC-26 subscales. The LCGA is a flexible methodology to model patient longitudinal trajectories from unobserved subpopulations (i.e., latent trajectory classes) with patient variation in growth parameters (e.g., intercept and slope) that are expressed with random effects. Another advantage of this methodological approach is that predictors of longitudinal trajectory membership could be identified within the LCGA framework by directly introducing these independent variables in the model. This permitted to quantify the net effect of each predictor whilst adjusting for the other ones and, thus, to better and more validly identify the best predictors of longitudinal trajectory membership (for a brief and clear overview of LCGA, see Jung & Wickrama, 2008)[95]. The LCGA approach has been efficiently adopted to identify trajectories of change over time in quality of life, symptomatology, and adjustment to several types of illness, such as heart failure[96], depression[97], low back pain[98], and breast cancer[99].

Non-linear LCGA consisting of intercept, slope and quadratic growth parameters were performed with Mplus 8.2. Missing urinary incontinence and sexual dysfunction across waves were handled using a robust full information maximum likelihood (FIML) estimation procedure. To determine the number of classes to be extracted, we primarily considered the Lo-Mendell-Rubin likelihood ratio test (LMR-LRT) following by other statistical considerations, such as a successful convergence (i.e., no local maximum likelihood), high

entropy value close to 1 (i.e., high precision and certainty in the classification), and total count within each classes above 1% (i.e., absence of classes with too few members). Specifically, the LMR-LRT compares the solution with k classes with the solution with k-1 classes; statistically significant values indicate that the broader solution (i.e., k classes) better fits the data than the more restricted k-1 classes solution. After determining the number of classes to be extracted for the urinary incontinence and sexual dysfunction, clinical and sociodemographic predictors of longitudinal change membership were introduced in the unconditional LCGA models via multinomial logistic regression. We compared the reference class (i.e., high levels of urinary incontinence or sexual dysfunction) with the other identified longitudinal trajectories to assess the discriminative power of each clinical and sociodemographic predictor in differentiating among the identified longitudinal trajectories. Specifically, pre-surgery urinary incontinence score, age, BMI (0=BMI less than 27; 1=BMI equal or greater than 27), diabetes (0=no diagnosis of diabetes; 1=diagnosis of diabetes) were introduced as predictors to explain membership in longitudinal trajectories of urinary incontinence. Pre-surgery sexual dysfunction score, age, and nerve sparing were introduced as predictors to explain membership in longitudinal trajectories of sexual dysfunction. Because Mplus does not accommodate categorical independent variables, nerve sparing was entered as two distinct dummy variables (i.e., unilateral and bilateral nerve sparing; no nerve sparing was the reference category). In each model, the worst longitudinal trajectory was chosen as the reference category in the multinomial regression model.

Finally, the association between membership in the two longitudinal trajectories of urinary incontinence and sexual dysfunction was assessed by considering the results of a Chi-square test and its related contingency table.

2.4.2 Results

Identification of Longitudinal Trajectories of Urinary Incontinence

LCGA was performed on the urinary incontinence scores of the EPIC-26 measured at the five time points of the present study. A five-class model with five different longitudinal

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trajectories was chosen because the LMR-LRT indicated that the five classes are significantly better than four (p =.039) and better than six (p =.266). Moreover, this five-class solution also displayed a high entropy level (.837) and total count within each class above 1% (min=4.65%; max=38.44%). Figure 7 reports the five identified longitudinal trajectories of urinary incontinence over time.
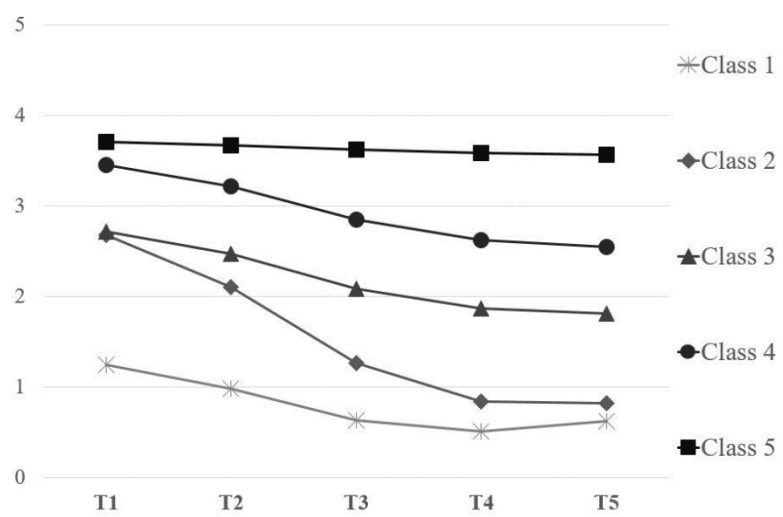
Figure 7: The five identified longitudinal trajectories of urinary incontinence

Patients in the first class (38.44% of the total count) showed the lowest initial status of urinary incontinence (intercept=1.25, p<.001) and a moderate recovery over time (slope=-0.29, p<.001; quadratic=0.03, p<.001). We labeled this longitudinal trajectory as "Class 1". As shown in Table 2, 51.4% of patients presented with biopsy Gleason score 6, while in 2.2% of cases was higher than 8. The majority of patients (67%) had a pre-surgical PSA between 4 and 10, and 76.1% had an ASA score between 2 and 3. The Charlson Index was lower than 1 in 78.4% of the sample. Moreover, 91.4% of patients who underwent RARP and belonging to this Class had no post-surgical complications. The "Class 2" encompassed 26.44% of patients with moderate initial levels of urinary incontinence (intercept=2.68, p<.001) and a sudden decrease of symptomatology over time (slope=- 0.62, p<.001; quadratic=0.05, p<.001). Eighty-five percent of patients belonging to Class 2 had a Gleason Score lower than eight, 73.1 % of them had a PSA index varying between 4 and 10, and 84.2% an ASA score of 2 or 3. Their Charlson Index was lower than 1 in 72.4% of the cases

and 89.6% of Class 2 had no complications after surgery (see Table 2). The third class (18.32% of the total count), labeled "Class 3", was characterized by moderate urinary incontinence at baseline (intercept=2.72, p<.001) and a moderate recovery over time (slope=- 0.27, p<.001; quadratic=0.02, p=.021). Almost 49% of patients presented with biopsy Gleason score 6, while in 1.2% of cases was 9 or 10 (see Table 2). The majority of patients (60%) had a pre-surgical PSA between 4 and 10, and 83.5% had an ASA score between 2 and 3. The Charlson Index was lower than 1 in 68.8% of the sample. Moreover, 88.8% of patients who underwent RARP and belonging to Class 3 had not post-surgical complications. The "Class 4" included 12.14% of patients with a high urinary incontinence at 45 after the RARP (intercept=3.46, p<.001) and a moderate recovery over time (slope=- 0.26, p<.001; quadratic=0.02, p=.059). Eighty-three percent of patients belonging to Class 4 had a Gleason Score lower than eight, 59.3% of them had a PSA index varying between 4 and 10, and 84.5% an ASA score of 2 or 3. Their Charlson Index was lower than 1 in 71.2% of the cases and 88.1% of Class 4 had not complications after surgery (see Table 7). The last class (4.65% of the total count) had the worst initial status of urinary incontinence (intercept=3.70, p<.001) with a flat and non-significant linear and quadratic trajectory (linear slope=- 0.03, p=.403; quadratic slope=0.00, p=.758). This class could be labelled "Class 5". As shown in Table 2, this Class showed a Gleason Score of 6 in 35% and 7 in 40% of the cases, respectively. Seventy-five percent of the patients belonging to Class 5 had a PSA index varying from 4 to 10, and 90% of them showed an ASA score of 2 or 3. The Charlson index was higher than 1 in 55% of the cases and men of this Class had post-surgical problems in 25% of the cases.

Table 7. Clinical Variables in identified Urinary clusters

Clinical Variables	Class 1 (%)	Class 2 (%)	Class 3 (%)	Class 4 (%)	Class 5 (%)
Gleason Score					
≤ 6	51.4	42.5	48.8	39.0	35.0
7	35.5	42.5	40.0	44.0	40.0
8	10.9	7.5	10.0	13.6	25.0
9-10	2.2	7.5	1.2	3.4	0

PSA Class					
Less than 4	14.6	7.5	18.8	11.9	10.0
4-10	67.0	73.1	60.0	59.3	75.0
More than 10	18.4	19.4	21.2	28.8	15.0
ASA Class					
1	23.9	15.8	16.5	15.5	10.0
2-3	76.1	84.2	83.5	84.5	90.0
Charlson Index					
<1	78.4	72.4	68.8	71.2	45.0
≥1	21.6	27.6	31.2	28.8	55.0
Complications					
No	91.4	89.6	88.8	88.1	75.0
Yes	8.6	10.4	11.2	11.9	25.0

Sociodemographic and Clinical Predictors of Longitudinal Trajectories of Urinary Incontinence

Then, the predictive role of clinical and sociodemographic variables to explain membership in longitudinal trajectories of urinary incontinence was assessed through multinomial logistic regression. Specifically, pre-surgery urinary incontinence score, age, BMI, and diabetes were introduced in this model as predictors of longitudinal change membership.

Because "Class 5" was the worst longitudinal trajectory of urinary incontinence over time, this class was chosen as the reference category in the multinomial regression model. Results showed that more elderly patients (B=-0.09, OR=0.92, p=.004) and higher levels of pre-surgery incontinence (B=- 1.30, OR=0.27, p=.003) had a lower chance to belong to "Class 2" compared to "Class 5". Moreover, compared to "Class 5", "Class 4" was characterized by overweight or obese patients (B=1.04, OR=2.83, p=.035). More elderly patients (B=-0.08, OR=0.92, p=.007) with higher levels of pre-surgery incontinence (B=- 2.27, OR=0.10, p=.015) had a lower likelihood of being included in "Class 1" than in "Class 5". Finally, compared to the worst longitudinal trajectory of urinary incontinence over time, prostate patients within "Class 3" were younger (B=- 0.08, OR=0.92, p=.025) and with less pre-RARP incontinence (B=- 1.11, OR=0.33, p=.007).

Diabetes was not helpful to distinguish between patients belonging to the five classes.

The analysed sociodemographic and clinical characteristics were not able to distinguish the membership between Class 2 and Class 3, even if they have the same characteristics before surgery but different trajectories afterwards.

Identification of Longitudinal Trajectories of Sexual Dysfunction

LCGA was performed on the sexual dysfunction scores over time. A three-class model with three distinct longitudinal trajectories was chosen because the LMR-LRT indicated that the three classes are significantly better than two (p<.001) and better than four (p=.404). Moreover, this three-class was also supported by a high entropy value (.913) and total count within each class above 1% (min=15.49%; max=59.92%). Figure 8 reports these identified longitudinal classes of change of sexual dysfunction over time.
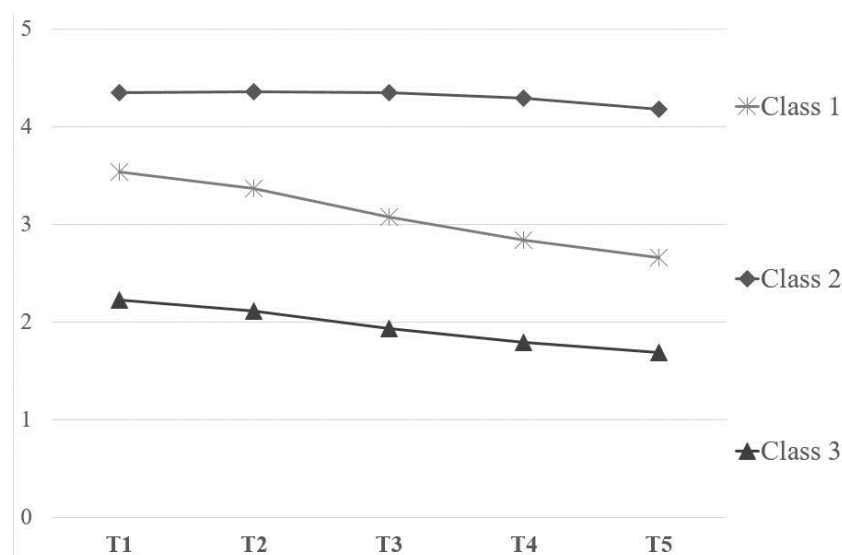
Figure 8: The three identified longitudinal trajectories of sexual dysfunction

Patients in the first class (24.59% of the total count) showed a medium initial level of sexual dysfunctionality (intercept=3.54, p<.001) and a moderate recovery over time (slope=- 0.18, p<.001; quadratic=0.01, p=.172). We labeled this class as "Class 1". As shown in Table 3, 55.1% of patients presented with biopsy Gleason score 6, while 44.9% of cases was between7 and 8. The majority of patients (71.2%) had a pre-surgical PSA between 4 and 10, and 77.6% had an ASA score between 2 and 3. The Charlson Index was lower than 1 in 72.9% of the sample. Moreover, 91.5% of patients who underwent RARP and belonging to this Class had not post-surgical complications. "Class 2" encompassed 59.92% of patients

with the higher levels of sexual impairment at baseline (intercept=4.34, p<.001) and a flat and non-significant recovery over time (slope=0.02, p=.123; quadratic=- 0.01, p=.002). Almost eighty-two percent of patients belonging to Class 2 had a Gleason Score lower than eight, 63.2 % of them had a PSA index varying between 4 and 10, and 84.2% an ASA score of 2 or 3. Their Charlson Index was lower than 1 in 69.4% of the cases and 87.5% of Class 2 had not complications after surgery (see Table 8). The third class (15.49% of the total count), labeled "Class 3", was characterized by the lowest levels of sexual dysfunction at 45 days after the RARP (intercept=2.23, p<.001) and a moderate recovery over time (slope=- 0.11, p=.046; quadratic=0.01, p=.420). Patients belonging to Class 3 showed a biopsy Gleason score of 6 in 66.2%, 7 in 26.8% and 8 in 7% of the cases, respectively. Seventy-five% of patients had a PSA index from 4 to 10 and an ASA score of 2 or 3. Eighty-six percent of patients had a Charlson index lower than 1, while almost 93% percent had not complications after RARP (See Table 8).

Table 8. Clinical Variables in identified Sexual clusters

Clinical Variables	Class 1 (%)	Class 2 (%)	Class 3 (%)
Gleason Score			
≤ 6	55.1	37.6	66.2
7	35.6	44.3	26.8
8	9.3	12.2	7.0
9-10	0	5.9	0
PSA Class			
Less than 4	14.4	13.2	8.3
4-10	71.2	63.2	75.0
More than 10	14.4	23.6	16.7
ASA Class			
1	22.4	15.8	24.6
2-3	77.6	84.2	75.4
Charlson Index			
<1	72.9	69.4	86.1
≥1	27.1	30.6	13.9
Complications			
No	91.5	87.5	93.1
Yes	8.5	12.5	6.9

Clinical Predictors of Longitudinal Trajectories of Sexual Dysfunction

Then, the predictive role of clinical and sociodemographic variables to explain membership in longitudinal trajectories of sexual dysfunction was evaluated through multinomial logistic regression. Specifically, pre-surgery sexual dysfunction score, age, and nerve sparing were introduced in this model as predictors of longitudinal change membership.

Because "Class 2" was the worst longitudinal trajectory of sexual dysfunction over time, this class was chosen as the reference category in this multinomial regression model. Results showed that more elderly patients (B=- 0.08, OR=0.93, p=.004) and a higher level of pre-surgery sexual symptoms (B=- 1.30, OR=0.27, p<.001) had a lower chance of belonging to the "Class 3" compared to the "Class 2". Nerve sparing procedure was not able to distinguish between patients belonging to "Class 2" and "Class 3". Again, compared to the "Class 2", the "Class 1" was characterized by patients with lower levels of pre-surgery sexual problems (B=- 0.89, OR=0.41, p<.001) and subjected to bilateral nerve sparing RARP (B=1.19, OR=3.29, p=.028). Age and unilateral nerve sparing RARP did not distinguish between patients belonging to "Class 2" and "Class 1".

Associations between Membership in Longitudinal Trajectories of Urinary Incontinence and Sexual Dysfunction

The results of the Chi-square test assessing the association between memberships in urinary incontinence and sexual dysfunction membership demonstrated that the two cluster membership tended to co-occur [X^2(8, N=478) = 60.20, p<.001]. Specifically, the adjusted residual reported in the contingency table (Table 9) demonstrated that patients belonging to the "Class 1" of sexual dysfunction had a low chance to be ascribed to the "Class 4" and "Class 5" and a high chance to be ascribed to the "Class 1" of urinary incontinence. We highlighted a symmetrical and opposite pattern of associations for the "Class 2" of sexual dysfunction; specifically, patients in this longitudinal trajectory were more likely to be ascribed to "Class 4" and "Class 5" while they had a low likelihood to belong to the "Class

1". Finally, patients in "Class 3" of sexual symptoms had a low likelihood to belong to "Class 3" and "Class 4" while showing a high probability to be ascribed in "Class 1".

Table 9. Contingency table between longitudinal trajectories' membership of urinary incontinence and sexual dysfunction (adjusted residuals within each cell are reported in Italics)

		Urinary Incontinence				
		Class 1	**Class 2**	**Class 3**	**Class 4**	**Class5**
Sexual Dysfunction	**Class 1**	56	34	21	6	1
		2.2	*0.2*	*0.4*	*- 2.8*	*- 2.1*
	Class 2	81	82	54	52	19
		- 5.8	*0.3*	*1.5*	*4.7*	*3.2*
	Class 3	48	18	5	1	0
		5.3	*- 0.6*	*- 2.4*	*- 3.1*	*- 1.9*

2.4.3 Discussion

This study identifies different longitudinal trajectories of patients with PC underwent RARP based on their initial status and change over time in urinary incontinence and sexual dysfunction.

Different trends for each of these two EPIC-26 subscales were identified: five and three classes were found for urinary incontinence and sexual dysfunction subscales, respectively. All but one of the trajectories of urinary incontinence showed a moderate recovery over one year after surgery. Only the class with the worst initial status showed a non-significant recovery over time: people who have a high level of urinary incontinence 45 days after surgery are likely to have a worse recovery. In fact, the small proportion of patients with high urinary incontinence rates at baseline either do not recover, or their symptomatology gradually decreases over time. On the contrary, patients with a low level of leaking urine after RARP have a faster, and sometimes sudden, recovery. According to the literature[88],

these different trends may be affected by sociodemographic and clinical variables, like age, pre-surgical condition, and BMI. Elderly and overweight patients may display higher level of incontinence 45 days after surgery and may have more problems in the recovery trajectories, while those with lower levels of pre-surgery continence seem to have greater chance to recover faster and report very small problems one year after RARP.

Nevertheless, the analysed sociodemographic and clinical variables were not always able to predict the membership among different classes. In particular, Class 2 and 3 showed the same characteristics before surgery but different trajectories afterwards: other variables should be included to distinguish the different classes already at T0. Among the considered predictors, no psychological factors were included: it would be necessary to deepen which aspects may impact these trends and predict patients' membership to the identified categories.

Similar to urinary incontinence, sexual dysfunction presents different classes of post-surgery condition and recovery. Patients with low and moderate problems 45 days after surgery can face a moderate linear recovery, while men with more significant impotence immediately after surgery may take a longer period to solve sexual dysfunctions. In fact, most of the patients display high level of impotence after RARP and with no recovery of their potency even after one year from surgery. Age and the pre-surgical sexual condition are important aspects to identify patients with difficulties in recovery from erectile dysfunction. In fact, elderly men and patients with sexual impairment before surgery are less likely to recover than the others. A recent study with a sample stratified by men's pre-operative scores of erectile function showed that each group statistically and differently improved in potency rates at consecutive follow-up visits up to 24 months, proving that the time of recovery varies along with patients' baseline characteristics[91]. Moreover, bilateral nerve-sparing surgical intervention seems to positively reduce post-surgery recovery.

The evaluation of the association between membership in the longitudinal trajectories of urinary incontinence and sexual dysfunction may help physicians in the identification of

patients with difficulties in the recovery of both symptoms. In fact, some of these patients reported both steady problems in sexual function and constant high levels of urinary incontinence over time. On the contrary, people with low rates in urinary incontinence more probably will also display less level of sexual potency. Sexual and urinary dysfunctions are the most common consequences after PC treatments[75] and the displayed association underlines the importance of investigating these aspects in clinical practice. In fact, the scientific literature shows that sexual life and urinary incontinence are strictly related and the most bothersome aspects of incontinence were its effects on partner relationship and sexual life[79,82,100].

These results identify urinary incontinence and sexual dysfunction as the most common and unsolved drawbacks after one year from RARP. Even if they show an overall improvement over time, one year after RARP no patients' class has a full recovery and most of the time scores down only a point in one year. For this reason, it would be important to analyze cancer survivors' recovery for a longer time in order to better describe the complete process of care[101,102]. Research studies on short and long side-effects pointed out that patients still suffer from erectile dysfunction, but have a good continence status, even after a median follow-up of 42 months after surgery[79]. Moreover, physical impairments negatively impact patients' level of distress, quality of life and life satisfaction even 2- or 3-years after diagnosis[86,103].

Clinical Implications

The identification of different longitudinal trajectories of patients with PC undergone RARP in urinary incontinence and sexual dysfunction provides new evidence on patients' recovery over the care process. This evidence may be important elements to be discussed during patient-physician relationship: urologists may adopt this information to help men make informed decisions in line with their individual preference and adjust their expectations about long-term sexual life. In fact, physicians' and patients' hopes of body function recovery do not always concur and great clarity would be needed[104,105].

Thanks to the adoption of a person-oriented approach, our results may be useful to identify patients at risk and typical trajectories of recovery, which are important prerequisites of patient-centered care and planned healthcare programs. A patient-centered approach related to multidisciplinary cooperation would be important to overcome medical barriers and empower patients, making them aware of their care pathway[106,107]. Along with personalized interventions and the development of eHealth platforms to enhance patient's health literacy and engagement[108–110], a new approach to the healthcare system would be needed. The implementation of a new healthcare system based on value would help set up predictive and individualized care pathways for each cancer diagnosis. The patient would be followed along the care process collecting psychological, medical outcomes and economic outcomes in order to implement predictive model of care[111–113].

Limitations

Several limitations of this study have to be considered. First of all, we were not able to conduct a growth mixture modeling (GMM) analysis instead of the LCGA, although a larger sample would have been necessary to conduct a GMM. In LCGA we set to 0 the intra-class variances of intercepts and slopes, providing a less accurate estimate of the latent trend of the dysfunctions' recovery [114]. Moreover, comorbidities and other possible psychological or medical predictors have not been collected. Finally, the measured outcomes were collected up to only one year after surgery: it would be important to extend the follow-ups, in order to better analyze patient's recovery of functions, which mostly lasts more than one year after treatments[86,88].

Therefore, our future directions would be to collect more information about patient's characteristics and psychological outcomes through the use of standardized questionnaires and semi-structured interviews to provide a more comprehensive framework of the patient care process.

2.5 Study 2a: Dimensionality and measurement invariance of the Italian version of the EORTC QLQ-C30 in postoperative lung cancer patients

Among a large number of developed instruments to evaluate patient well-being, the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) is the most used tool for assessing QoL in cancer-specific patients[115]. The EORTC QLQ-C30 (*Appendix 3*) consists of thirty self-reported questions assessing different aspects of patient functioning, global health status, and cancer-related symptoms. More specifically, it is composed of five multi-item functional scales (role, physical, cognitive, emotional and social functioning), three multi-item symptom scales (fatigue, pain, and nausea and vomiting), individual items concerning common symptoms in cancer patients (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties), and two questions assessing overall QoL. All of the multi-item scales and single-item measures range in a score from 0 to 100, where a high score represents a higher response level. Thus, a high score for a functional scale implicates a healthy level of functioning, while a high score for a symptom scale represents a worse level of symptoms[116]. The EORTC QLQ-C30 has been translated in over 110 languages and validated in many countries in different samples of cancer patients[117,118]. According to a cross-cultural project on a large and heterogeneous sample, the EORTC Quality of Life Group reported robust measurement properties across various countries and languages[119,120]. In Italy, the questionnaire has been validated only in breast and colon cancer patients[121–123], At the same time, other authors investigated the applicability of the EORTC QLQ-C30 structure, and positively demonstrated its invariance across different cancer sites[124]. Despite these psychometric properties, few scientific articles performed factor analysis for validating this tool in lung cancer patients, a clinical area in which the EORTC QLQ-C30 is the most used instrument to report patient well-being through the different phases of disease[125]. To our knowledge, no published articles investigated the psychometric properties and the measurement invariance of the Italian version of the

EORTC QLQ-C30 in lung cancer patients. In fact, only four studies measured Quality of Life in Italian lung cancer patients through the administration of the EORTC QLQ-C30. Two of them were international studies and involved several countries, with all of them focusing on non-small cell lung cancer[126–129].

The purpose of the current study was to evaluate the factor structure proposed by Costa and colleagues[124] for the EORTC QLQ-C30 in a sample of postoperative lung cancer patients that underwent lobectomy surgery. Moreover, its measurement invariance across patients of varying age, gender, and undergoing robotic or traditional surgery was also evaluated. The testing of measurement invariance is a necessary step to further evaluate any inter-individual differences.

2.5.1 Material and methods

Participants and procedure

An Italian sample of 167 patients with lung cancer who were also undergoing lobectomy was recruited for the Value-Based Project at the European Institute of Oncology in Milan between October 2015 and October 2017. Patients were included in the study if they: 1) were diagnosed with lung cancer, 2) were native Italian speakers, 3) referred to the Value-Based Project and 4) did not have neurological or psychopathological problems. They completed the EORTC QLQ-C30 after 30 days from surgery[116,122]. During the doctor's post-operative visit, a trained nurse distributed the questionnaire to the patients and they completed it using paper and pencil. Informed consent was provided and signed by each participant. Participation in the study was voluntary and at each moment, patients could withdraw their consent. The study was developed in accordance with the principles stated in the Declaration of Helsinki (59th WMA General Assembly, Seoul, 2008) and was approved by the European Institute of Oncology Ethical Committee at the European Institute of Oncology, Milan.

Statistical Analysis

All statistical analyses were performed using the Maximum Likelihood with Robust Standard Errors (MLR) estimation method with Mplus 8.2[130]. The MLR estimator is robust to strong departures from univariate and multivariate normality of observed variables. The EORTC QLQ-C30 comprises nine multiple-item dimensions and six single items. In the first step, the proposed model for the EORTC QLQ-C30 was assessed through CFA. Specifically, as reported in Figure 9, the measurement model included the nine multiple item dimensions of Physical functioning (5 items), Role functioning (2 items), Emotional functioning (4 items), Social functioning (2 items), Cognitive functioning (2 items), Pain (2 items), Fatigue (3 items), Nausea and vomiting (2 items), and Overall health and quality of life (2 items). Following Costa and colleagues[124], the six single-item dimensions (i.e., dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) were omitted from the tested model. For ease of interpretation, the covariances among latent dimensions of QoL were not reported in figure, but they were all estimated in the analyses.
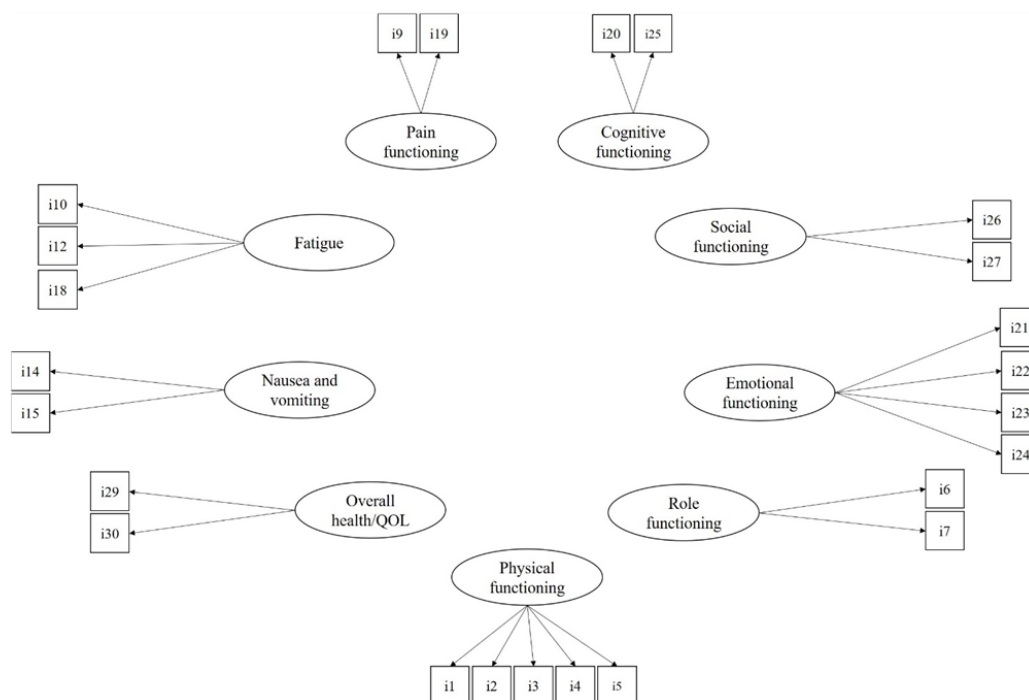
Figure 9: The measurement model for the EORTC QLQ-C30.

Note: for ease of interpretation, covariances among latent factors are not reported but estimated in the CFA model

Model fit was assessed by considering five main fit indices. Specifically, a good-fitting model was indicated by: a non-significant χ^2, a root mean square error of approximation (RMSEA) below 0.06, a standardized root mean square residual (SRMR) below 0.80, a comparative fit index (CFI) and a Tucker Lewis Index (TLI) above 0.90[64]. Moreover, the 90% confidence interval for RMSEA was considered to test the null hypothesis of poor model fit. Specifically, a good-fitting model was indicated by the upper limit below 0.08 and the lower limit close to zero. Finally, we considered the probability of close fit (PCLOSE) as well, a one-sided test of the null hypothesis that the model has a close fit (i.e., RMSEA equals 0.05). P-value above 0.50 indicated a good-fitting model[131].

Then, measurement invariance was evaluated by considering Differential Item Functioning (DIF). DIF is a prerequisite for a valid and meaningful comparison of levels of QoL across gender, age, and type of surgery (robot-assisted vs. traditional surgery). Specifically, a Multiple Indicators-Multiple Causes (MIMIC) was performed to assess differences in the measurement model due to age, gender, and type of surgery. A MIMIC model was performed because it has specific advantages over Multiple-group Confirmatory Factor Analysis (MCFA) in evaluating measurement invariance. Specifically, compared to MCFA, the MIMIC model permits to: assess differences in the measurement model due to several confounding variables; simultaneously evaluate the role of dichotomous (i.e., robot-assisted vs. not robot-assisted surgery and gender) and continuous variables (i.e., age); include directly in the model continuous variables without median-splitting, mean-splitting or subjective categorization, and test measurement invariance even with small sample size. Thus, mainly because of the low sample size, we preferred the MIMIC model over the MCFA to assess the structural invariance of the EORTC-QLQ-C30. In the last decade, MIMIC model had been adopted to validly test measurement invariance of self-report measure of quality of life in asthma[132] and pediatric patients[133], life satisfaction[134],

dispositional optimism[135], protective behavioral strategies[136], adolescent burnout[137], and depression[138].

The MIMIC Model included the measurement model (i.e., the EORTC QLQ-C30 factor structure) plus a structural model assessing DIF. This structural model estimated the effect of covariates of gender, age, and type of surgery on latent dimensions of QoL and, thus, evaluated differences in these latent factors due to the three considered covariates. The structural model included the direct effects of these three covariates on items as well. In a first step, these direct effects fixed at zero. Then, modification indices were examined to ascertain whether the estimation of any of these direct effects would improve model fit. Estimation of direct effects was performed with a stepwise approach: the constraint that resulted in the greatest change of χ^2 (i.e., highest value of the modification index) were firstly estimated. We then continued at freely estimating one direct effect at time until any modification was relevant (i.e., $\Delta \chi^2 > 3.84$). Each significant direct effect was interpreted as an indication of DIF: the likelihood to endorse an item was conditional to the specific covariate involved in the direct effect. For example, if the direct effect of age on item 1 was significant and positive, then the likelihood of endorsing this item differed between patients of different age and, specifically, younger people had lower chance to endorse this item. Thus, measurement invariance may be strongly impaired when high degree of DIF is ascertained. Age was treated as a continuous variable, whereas gender (i.e., Male = 0; Female = 1) and type of surgery (i.e., Not robot-assisted surgery = 0; Robot-assisted surgery = 1) were binary variables.

2.5.2 Results

Sample and item characteristics

Participants had a mean age of 66.69 ± 7.70 and 100 (59.9%) of them were males. The sample underwent lobectomy surgical procedure (N=54; 32.3% with robot-assisted surgery; N=113; 67.7% with not robot-assisted surgery). Other clinical variables are reported in Table

9. Descriptive statistics of item response (mean, standard deviation, minimum and maximum) are reported in Table 10.

Table 9. Clinical sample characteristics

	Sample (%)
ASA Class	
1	3.6
2-3	96.4
Charlson Index	
<1	60.5
≥1	39.5
Robot-assisted surgery	
No	26.4
Yes	55.9
Complications	
No	67.1
Yes	32.9

Table 10. Descriptive statistics of item response

Items	M	SD	Min	Max
i1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? *Ha difficoltà nel fare lavori faticosi, come sollevare una borsa della spesa pesante o una valigia?*	2,16	0,85	1	4
i2. Do you have any trouble taking a long walk? *Ha difficoltà nel fare una lunga passeggiata?*	2,171	0,87	1	4
i3. Do you have any trouble taking a short walk outside of the house? *Ha difficoltà nel fare una breve passeggiata fuori casa?*	1,396	0,68	1	4
i4. Do you need to stay in bed or a chair during the day? *Ha bisogno di stare a letto o su una sedia durante il giorno?*	1,799	0,76	1	4
i5. Do you need help with eating, dressing, washing yourself or using the toilet? *Ha bisogno di aiuto per mangiare, vestirsi, lavarsi o andare in bagno?*	1,085	0,37	1	4
i6. Were you limited in doing either your work or other daily activities? *Ha avuto limitazioni nel fare il Suo lavoro o i lavori di casa?*	1,915	0,84	1	4
i7. Were you limited in pursuing your hobbies or other leisure time activities? *Ha avuto limitazioni nel praticare i Suoi passatempi- hobby o altre attività di divertimento o svago?*	1,857	0,82	1	4
i9. Have you had pain? *Ha avuto dolore?*	1,883	0,85	1	4
i10. Did you need to rest? *Ha avuto bisogno di riposo?*	2,085	0,73	1	4
i12. Have you felt weak? *Si è sentito debole?*	2,037	0,81	1	4
i14. Have you felt nauseated *Ha avuto un senso di nausea?*	1,421	0,69	1	4

i15. Have you vomited? *Ha vomitato?*	1,049	0,29	1	4
i18. Were you tired? *Si è sentito stanco?*	2,078	0,74	1	4
i19. Did pain interfere with your daily activities? *Il dolore ha interferito con le Sue attività quotidiane?*	1,723	0,79	1	4
i20. Have you had difficulty concentrating on things, like reading a newspaper or watching television? *Ha avuto difficoltà a concentrarsi su cose come leggere un giornale o guardare la televisione?*	1,265	0,56	1	4
i21. Did you feel tense? *Si è sentito teso?*	1,719	0,74	1	4
i22. Did you worry? *Si è preoccupato?*	1,768	0,79	1	4
i23. Did you feel irritable? *Si è sentito irritabile?*	1,643	0,74	1	4
i24. Did you feel depressed? *Si è sentito depresso?*	1,675	0,86	1	4
i25. Have you had difficulty remembering things? *Ha avuto difficoltà a ricordare le cose?*	1,394	0,63	1	4
i26. Has your physical condition or medical treatment interfered with your family life? *Le Sue condizioni fisiche o il Suo trattamento medico hanno interferito con la Sua vita familiare?*	1,429	0,65	1	4
i27. Has your physical condition or medical treatment interfered with your social activities? *Le Sue condizioni fisiche o il Suo trattamento medico hanno interferito con le Sue attività sociali?*	1,582	0,73	1	4
i29. How would you rate your overall health during the past week? *Come valuterebbe in generale la Sua salute durante gli ultimi sette giorni?*	4,597	1,03	2	7
i30. How would you rate your overall quality of life during the past week? *Come valuterebbe in generale la Sua qualità di vita durante gli ultimi sette giorni?*	4,636	1,14	2	7

Assessing the Factor Structure

The proposed measurement model for the EORTC QLQ-C30 showed a good fit [χ^2(216, N = 167) = 301.48; RMSEA = 0.05; 90% C.I. of RMSEA = 0.04 – 0.06; PCLOSE = .555; CFI = 0.95; TLI = .93; SRMR = 0.05). The standardized loadings are displayed in Table 11. As reported, all the items had significant loadings and high loadings ranging from .36 to 1.08, except for i5 (λ = .17; S.E. = .07; $p < .05$) and i15 (λ = .13; S.E. = .12; $p > .05$). Specifically, while high scores of pain, fatigue, nausea and vomiting, and physical, role, cognitive,

emotional, and social functioning indicated high levels of impairment, high values of overall health and quality of life denoted high levels of health-related quality of life.

Table 11. Standardized factors loading, standard errors and significance for the measurement model of the EORTC QLQ-C30.

	PF	RF	PA	FA	NV	CF	EF	SF	QL
i1	.63 (.06)***								
i2	.68 (.06)***								
i3	.51 (.07)***								
i4	.55 (.07)***								
i5	.17 (.07)*								
i6		.75 (.05)***							
i7		.62 (.07)***							
i9			.65 (.06)***						
i19			.75 (.06)***						
i10				.55 (.06)***					
i12				.66 (.06)***					
i18				.65 (.06)***					
i14					.40 (.17)*				
i15					.13 (.12)				
i20						.47 (.09)***			
i25						.36 (.09)***			
i21							.60 (.06)***		
i22							.53 (.08)***		
i23							.54 (.08)***		
i24							.64 (.08)***		
i26								.51 (.08)***	
i27								.67 (.07)***	

		.92 (.07)***
i29		
i30		1.08 (.07)***

Note: PF = Physical functioning; RF = Role functioning; PA = Pain; FA = Fatigue; NV = Nausea and vomiting; CF = Cognitive Functioning; EF = Emotional functioning; SF = Social functioning; QL = Overall health and quality of life

Table 12 displays correlations among the nine latent dimensions of QoL. Significant correlation coefficients ranged from .24 to .85 in absolute values. These correlations could be interpreted as measure of effect size of the associations among latent factors. Following suggestion by Cohen[139], the magnitude of these coefficients were interpreted as: weak (above .10), moderate (above .30), and strong (above .50). Specifically, weak associations were reported between cognitive functioning and physical functioning ($r = .29$), emotional functioning and nausea/vomiting ($r = .29$), and nausea/vomiting and health-related QoL ($r = -.24$). A grand total of eighteen correlations were large in magnitude. Physical functioning and fatigue were the latent dimensions displaying the higher number of strong correlations with other factors of QoL. Specifically, physical functioning displayed strong associations with pain ($r = .54$), fatigue ($r = .85$), health-related QoL ($r = -.67$), role ($r = .77$), cognitive ($r = .51$), emotional ($r = .50$), and social functioning ($r = .50$). Fatigue showed strong associations with health-related QoL ($r = -.68$), pain ($r = .63$), nausea/vomiting ($r = .51$), physical ($r = .85$), role ($r = .76$), cognitive ($r = .59$), emotional ($r = .62$), and social functioning ($r = .51$). Finally, role functioning was the latent dimension of QoL most strongly associated with health-related QoL ($r = -.72$).

Table 12. Correlations (and their significance) among the nine latent dimensions of the EORTC QLQ-C30.

	PF	RF	PA	FA	NV	CF	EF	SF	QL
PF	-								
RF	.77***	-							

	PF	RF	PA	FA	NV	CF	EF	SF	QL
PA	.54***	.71***	-						
FA	.85***	.76***	.63***	-					
NV	.34***	.43*	.46***	.51***	-				
CF	.51***	.48***	.29**	.59***	.30	-			
EF	.50***	.52***	.45***	.62***	.29*	.41**	-		
SF	.50***	.54***	.37***	.51***	.08	.50***	.46***	-	
QL	-.67***	-.72***	-.57***	-.68***	-.24*	-.51***	-.42***	-.43***	-

Note: PF = Physical functioning; RF = Role functioning; PA = Pain; FA = Fatigue; NV = NAuese and vomiting; CF = Cognitive Functioning; EF = Emotional functioning; SF = Social functioning; QL = Overall health and quality of life

MIMIC Analysis of Measurement Invariance

After entering age, gender, and type of surgery in the model, goodness of fit slightly remained substantially unchanged [χ^2(261, N = 167) = 385.65; RMSEA = 0.05; 90% C.I. of RMSEA = 0.04 − 0.06; PCLOSE = .299; CFI = 0.93; TLI = .91; SRMR = 0.05]. The standardize factor loadings ranged from .15 to 1.01. Some significant influences of the three covariates on latent factors of QoL were reported. Specifically, type of surgery was responsible for differences in nausea/vomiting (β = -.52; S.E. = .22; p < .05), pain (β = -.32; S.E. = .15; p < .05), and physical (β = -.39; S.E. = .15; p < .01), role (β = -.46; S.E. = .16; p < .01), cognitive (β = -.31; S.E. = .15; p < .05), and social functioning (β = -.36; S.E. = .15; p < .05).

The inspection of modification indices suggested that model fit would be improved by freely estimated the direct effect of age on item 1 (β = -.03; S.E. = .01; p < .001). After the estimation of this effect, the model still showed a good fit [χ^2(260, N = 167) = 368.42; RMSEA = 0.05; 90% C.I. of RMSEA = 0.04 − 0.06; PCLOSE = .491; CFI = 0.94; TLI = .92; SRMR = 0.05]. No other modification indices were relevant.

After controlling for this DIF, some significant influences of the three covariates on latent factors of QoL were reported. Specifically, these influences were the same as the ones

reported in the previous MIMIC model (i.e., the model not freely estimating direct effects of covariates on items). Specifically, type of surgery was responsible for differences in nausea/vomiting (β = -.52; S.E. = .22; p < .05), pain (β = -.32; S.E. = .15; p < .05), and physical (β = -.38; S.E. = .15; p < .01), role (β = -.46; S.E. = .16; p < .01), cognitive (β = -.31; S.E. = .15; p < .05), and social functioning (β = -.36; S.E. = .15; p < .05). The only exception was that age directly influenced physical functioning (β = .03; S.E. = .01; p < .01). Thus, by comparing this final model with the previous one we may conclude that any bias due to DIF is only minimal and not accounting for DIF it may have only trivial consequences for the assessment of physical functioning (i.e., the magnitudes of age differences in physical functioning were comparable across the two models).

2.5.3 Discussion

This study represents an evaluation of the dimensionality and measurement invariance of the Italian version of the EORTC QLQ-C30 in a sample of patients with lung cancer who underwent lobectomy surgery. Our results demonstrated the validity of the factor structure proposed by Costa and his colleagues[124] and thus suggested that the EORTC QLQ-C30 could be used as a valid measure of quality of life in lung cancer patients undergoing lobectomy. In a previous study, Costa and his colleagues[124] proposed and supported this measurement model in a sample of cancer patients coming from fourteen countries all over the World and considering all the types of cancer(breast, colorectal, gynaecological, head and neck, lung, oesophagus/stomach, and prostate cancer). Compared to a previous trial on lung cancer patients assessing the changes in QoL over time[140], this study represents the first attempt on an Italian sample to evaluate the dimensionality and interindividual differences of patients' QoL with different sociodemographic and clinical characteristics. Another study[141] analyzed previously DIF on advanced cancer patients, while the present validation article was conducted on lung cancer patients with a primitive diagnosis.

The questionnaire comprises nine different dimensions. While one factor assesses 'overall health and health-related quality of life', the remaining eight factors measure distinct

symptoms and functioning, namely nausea/vomiting, pain, fatigue for the symptoms' subscales, and physical, role, emotional, cognitive, and social functioning for the functioning subscales. All nine subscales were significantly and strongly loaded by their relative items. The only exception was nausea and vomiting dimension: one out of its two items exhibited a non-significant and very low loading on its factor. Further research is needed to better assess the validity of this subscale in evaluating symptoms of nausea and vomiting in lung cancer patients and, if necessary, to develop more reliable items to evaluate this kind of adverse events.

Moreover, this study is the first one to evaluate the psychometric properties of the Italian version of the EORTC QLQ-C30 in lung cancer patients and assess its measurement invariance and DIF due to age, gender and robot-assisted versus not robot-assisted surgery. The presence of measurement invariance is one of the necessary steps in efficient and reliable evaluation of interindividual differences in QoL within samples of lung cancer patients and it represents a prerequisite to validly compare levels of overall health across patients of different genders and genders undergoing lobectomy with or without robot-assisted surgery. Our main results attested that only one item displayed a trivial DIF. Specifically, compared to younger patients, the elderly were more likely to endorse Item 1 (i.e., "Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?") on a 4-point scale (i.e., 1 = "Not at all"; 2 = "A little";3 = "Quite a bit"; 4 = "Very much"). However, the magnitude of this DIF was very small.

Finally, the last step in the evaluation of DIF involved the assessment of mean differences of nine latent scores of QoL across patients of different gender, varying age, and underwent robot-assisted or traditional surgery. The main aim of this analysis was to ascertain whether not controlling for DIF may lead to consequences for the assessment of QoL (i.e., mean differences in QoL differ when controlling or not controlling or DIF). These results highlighted that the DIF had only an irrelevant effect on the estimation of differences in latent means of QoL among patients. Accidentally, the results coming from this last step also

highlighted that younger patients displayed higher levels of physical functioning than elderly ones and that robot-assisted surgery may promote better QoL one month after surgery. Specifically, compared to patients undergoing traditional surgery, people treated with robot-assisted surgery displayed lower pain, nausea and vomiting, as well as better physical, role, cognitive, and social functioning. This latter result is consistent with empirical evidence showing that lung cancer patients treated with robotic thoracic surgery reported reduced postoperative pain and complications, fewer functional impairments, and a lower need of blood transfusions[142,143]. However, it's noteworthy that the main aim of this analysis was to assess the magnitude and the influence of DIF on mean differences of the nine latent scores of QoL; we did not aim at assessing differences due to age, gender, and type of surgery on patients' QoL. Moreover, since we did not balance the baseline characteristics (i.e, QoL itself) between patient underwent robot-assisted or traditional surgery, these results may not be interpreted in a casual way.

Limitations

Current results may be considered in light of some main limitations. Specifically, it was not possible to test convergent and/or divergent validity of the EORTC QLQ-C30 due to a lack of other self-report measures of patients' well-being. Nevertheless, a previous Italian validation of the questionnaire reported a substantial convergent validity[122], even though not in lung cancer patients. Finally, these statistical analyses must be taken with caution due to the relatively small sample size. Specifically, as highlighted by Kline (2015), the median of typical sample sizes in structural equation modeling studies is about 200 cases. Thus, our sample size of 167 lung cancer patients is slightly below this common standard. However, lower sample sizes are commonly recruited when the specific population being studied is restricted in size and it is difficult to reach higher sample sizes[144]. Thus, while the low sample size may represent a limit of our study, this size is a direct consequence of our target population. Because of this small sample, structural invariance of the EORTC QLQ-C30 was assessed by performing MIMIC model and DIF analysis which, compared to MCFA,

permit to better test measurement invariance even with small sample size. Future research collecting larger samples would be needed to further assess the factor structure of the EORTC QLQ-C30 in lung cancer patients underwent lobectomy with or without robot-assisted surgery.

Despite these limitations, our findings attested the goodness of the nine-factor structure of the Italian version of the EORTC QLQ-C30 in lung cancer patients and its measurement invariance in assessing QoL in patients with varying ages, genders, undergoing lobectomy with or without robot-assisted surgery. This is also the first study validating a QoL questionnaire on lung cancer patients. In fact, other scales have not been already validated among Italian lung cancer samples. Additionally, the EORTC QLQ-C30 assesses more dimensions related to a cancer diagnosis than other questionnaires. As a practical consequence, we advise that nine distinct scores of overall health, pain, fatigue, nausea/vomiting, physical, social, role, emotional, and cognitive functioning should be computed for evaluating lung cancer patients' QoL in future research and clinical practice. The valid and reliable assessment of adverse events and functioning in lung cancer patients is a relevant and prognostic factor in the patient's recovery. In fact, patient survival is highly affected by treatment side-effects such as fatigue, loss of appetite, dyspnea, and coughing, as well as physical, psychological, cognitive and social functioning[145–147]. The EORTC QLQ-C30 may help healthcare stakeholders in measuring and monitoring QoL in both clinical and research fields. In particular, QoL in lung cancer has been studied to understand patients' health status during processes aimed to stop smoking and how it may influence patients' preferences in medical decision-making. It was also used to better investigate possible long-term effects of rumination on patients' recovery and well-being[148,149]. In a patient-centered approach, the measurement of QoL would be also important to assess how individual differences and cognitive processes may influence patient well-being in different medical conditions[106,107,150].

In conclusion, the EORTC-QLQ-C30 is a useful and valid self-report tool and it can be used to assess interindividual differences of QoL in lung cancer patients in both clinical and research contexts.

2.6 Study 2b: One-year Quality of Life trends in early stage lung cancer patients after lobectomy

Lung cancer is the most common cancer in both genders and the first cause of cancer death worldwide. Lung cancer trends are different among countries: Europe has lower trends than America[41,151,152]. In Europe, the LucE Report (2016) stated that "more than 312,000 people were affected by lung cancer every year in the EU"[153]. In Italy, both the incidence and mortality rates are decreasing for men and increasing for women[154].

Primary malignant lung cancers are classified into two different categories: non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC); most lung cancer patients (about 80%) are diagnosed as NSCLC. Providing an overall 5-year survival rate of 55-77%, a resection surgical intervention is the recommended treatment for early stage NSCLC[147]. Late diagnosis, comorbidities, and old age often impact on treatment possibilities, by reducing the therapeutic options and affecting patients' Quality of Life (QoL)[155–157]. Therefore, treatment efficacy, patient survival, and QoL are strictly related and mutually reinforcing. In this perspective, the QoL measurement is necessary to help the stakeholders having a more complete framework of patient's recovery and improving the decision-making process of the right treatment without being affected by cognitive biases[146,158,159].

The scientific literature shows indeed that Health-Related Quality of Life (HRQoL) outcome, before and after surgery, is an important predictor of patient's recovery and survival in lung cancer patients[146,160,161]. A systematic review (2009)[162] analyzing this association, reported that most of the included articles indicate overall QoL, functional dysfunctions, and symptoms (e.g. pain, fatigue, and appetite loss) - adjusted for different sociodemographic and clinical characteristics - as prognostic factors of patients' survivorship. In fact, a high survival rate is associated with better patients' well-being, higher

motivation, and engagement in doing physical activities, and greater pulmonary function[163–166]. Monitoring patients' QoL after surgery and identifying its predictors is therefore important to guarantee better survivorship: several studies showed that patients who underwent surgery often reported a worsening in QoL after treatment[167]. In particular, Yang and colleagues (2012) showed that 35% of long-term lung cancer survivors had a significant decline in overall QoL related to a worse level of fatigue, pain, dyspnea, appetite, and cough[168]. Also disturbed sleep and distress affect QoL over time[169]. Another article (2013) analyzed demographic and clinical characteristics as predictors of QoL in lung cancer survivors and reported that younger participants showed more fatigue, dyspnea, and stress for financial problems. Patients with cancer-related comorbidities reported less severe dysphagia, nausea and vomiting[163]. According to the type of surgery, patients take 6 to 12 months to return to their preoperative HRQoL status[170,171]. The video-assisted thoracoscopic surgery (VATS) implies a faster recovery and better QoL in NSCLC patients than the thoracotomy one year after surgery[172]. Moreover, patients undergoing VATS were faster released from the hospital and reported less post-operative pain and complications than those who underwent traditional thoracotomy[173].

To our knowledge, only one previous research article studied the trajectories of lung cancer patients' QoL for a two-year period after surgery. Kenny et al. (2008)[167] showed that 65% of the recruited sample survived for 2 years after surgery and in that period of time HRQoL improved for patients with no recurrence, despite half of them continued to experience severe symptoms and functional limitations[167]. Nevertheless, the authors did not stratify for surgery type and did not study which sociodemographic or clinical characteristics may predict the QoL trend over time. For this reason, the aim of the study is to identify one-year trends of lung cancer patients' QoL after robot-assisted or traditional surgery and investigate whether clinical (e.g. pre-surgery QoL, type of surgery, and perioperative complications) and sociodemographic variables (e.g. age) may predict these trends.

2.6.1 Materials and Methods

Participants and Procedure

An Italian sample of 176 patients who underwent pulmonary lobectomy using the robotic-assisted approach or traditional open technique for lung cancer and participated in the Value-Based Project were enrolled at the European Institute of Oncology in Milan between October 2015 and November 2017. Patients were included into the study if they: 1) were diagnosed with primary early stage NSCLC (stage I and II), 2) were native Italian speakers, 3) were candidate to pulmonary lobectomy, and 4) had not neurological or psychopathological problems. Patients with cancer recurrences or with a previous thoracic surgical treatment were excluded from the study. All eligible patients were firstly asked to give written informed consent and then were asked to complete the EORTC QLQ-C30 questionnaire. They completed the EORTC QLQ-C30 at the pre-hospitalization (t0), 30 days (t1), 4 months (t2), 8 months (t3) and 12 months (t4) after lobectomy surgery.

Sociodemographic (i.e. age and gender) and clinical (i.e., perioperative complications: 0 = No perioperative complications; 1 = Perioperative complications; Type of surgery: 0 = Traditional lobectomy; 1 = Robot-assisted lobectomy) variables were also collected. Patients' sociodemographic and clinical characteristics are described in Table 13.

Table 13. Baseline characteristics of participants

Variables	Descriptive statistics
Age, years [mean (SD)]	66.71 (7.68)
Gender [N (%)]	
Female	70 (39.8%)
Male	106 (60.2%)
Type of surgery [N (%)]	
Traditional lobectomy	117 (66.5%)
Robot-assisted lobectomy	59 (33.5%)

Perioperative complications [N (%)]	
Yes	59 (33.5%)
No	117 (66.5%)
Education [N (%)]	
< High school	70 (39.7%)
High school or equivalent	73 (41.5%)
> High school	22 (12.5%)
Unknown	11 (6.3%)

Most patients have completed data at every follow-up (55.7%). The 18.2% had missing data at one follow-up, 14.8% at two follow ups, and 11.4% at three follow-ups. All data were collected and analyzed by a multidisciplinary team of the Value-Based Project. The study was developed in accordance with the principles stated in the Declaration of Helsinki (59th WMA General Assembly, Seoul, 2008) and was approved by the European Institute of Oncology Ethical Committee at the European Institute of Oncology, Milan. The participation in the study was voluntary and the patients could withdraw their consent at any time.

Measures

The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) is the most used tool for measuring QoL in lung cancer patients[115,174].

The EORTC QLQ-C30 consists of thirty self-reported questions assessing different aspects of patient functioning, global health status, and cancer-related symptoms. More specifically, it is composed of five multi-item functional scales (role, physical, cognitive, emotional and social functioning), three multi-item symptom scales (fatigue, pain, and nausea and vomiting), individual items concerning common symptoms in cancer patients (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties), and two questions assessing overall QoL. All of the multi-item scales and single-item measures range in a score

from 0 to 100Specifically, a high score for a functional scale and overall QoL implicates a healthy level of functioning and global health status, while a high score for a symptom scale represents worse symptomatology[116].

Statistical Analysis

Analyses were conducted using SPSS (Statistical Package for the Social Sciences), version 25. Individual growth curve (IGCs) models with the SPSS MIXED procedure were performed to evaluate trends of post-operative QoL across time and to assess the influence of pre-surgery QoL, type of surgery, perioperative complications and age on trends of QoL. IGC has several advantages in analyzing longitudinal data over traditional statistical methodologies, such as generalized linear models or analysis of variance. Specifically, ICG models allow one to validly analyze data that, as longitudinal data, violates the assumption of independence of observations. ICG models were performed by following guidelines by Singer and Willet (2003)[175] and Shek and Ma (2011)[176] to validly assess longitudinal trends and interindividual differences in intraindividual changes over time. Specifically, the data were analyzed by using mixed effect models with maximum likelihood (ML) estimation. This method allowed to model individual change over time, determine the shape of the growth curves, and explored systematic differences in change by examining the effects of covariates (i.e., pre-surgery QoL, type of surgery, perioperative complications, and age) on QoL initial status and rate of growth. Each of the 15 EORTC-QLQ-C30 dimensions was analyzed separately in four consecutive steps.

In the first step, an unconditional mean model (i.e., Model 1) was tested. This is a one-way ANOVA model with a random effect with no predictors included. It served as a baseline model and assessed the intraclass correlation coefficient (ICC). ICC describes the amount of variance in each of the QoL dimensions that is attributed to differences between patients and it evaluates the necessity of performing mixed model instead of traditional methods (e.g., ANOVA). Generally, ICC of 0.25 or above indicates the necessity of performing longitudinal analysis with repeated measure mixed models.

The second step involved performing an unconditional linear growth model (Model 2) that explored linear individual variations in trends of QoL over time and served as a baseline model to assess whether the growth curve of QoL was linear or curvilinear. In the third step, an unconditional quadratic growth model (Model 3) was performed to assess whether the rate of change accelerated or decelerated across time following a parabola-shape.

Random effect for intercept was estimated in all the models; random effect for linear change was estimated as well in Model 2 and Model 3. All these models were performed by fitting an unstructured (UN) covariance matrix for the random effects. Akaike Information Criterion (AIC) and -2log likelihood (-2LL) were considered to ascertain which of these three models were more appropriate to describe the change of each of the QoL dimensions over time. Specifically, the best fitting model was indicated by lower values of AIC. Moreover, a statistically significant likelihood ratio test between a smaller model (i.e., lower number of estimated effects/parameters) versus a more complex model indicated that the larger model provided a significant improvement in model fitting over the smaller one. Then, the best fitting model was subsequently retained and tested in the following steps. Specifically, in the last step, conditional models were performed to test whether pre-surgery QoL, age, type of surgery, and perioperative complications influenced initial QoL status at t1, linear growth rate, and quadratic change. Continuous variables (i.e., age and pre-surgery QoL) were grand mean centered, whereas perioperative complications and type of surgery were dummy coded (i.e., perioperative complications: 0 = No perioperative complications, 1 = Perioperative complications; Type of surgery: 0 = Traditional lobectomy, 1 = Robot-assisted lobectomy). Three different covariance structure models were performed to assess the error covariance structure: Model 4, conditional model with unstructured (UN) covariance structure, Model 5 conditional model with compound symmetry (CS) covariance structure, and Model 6, conditional model with first-order autoregressive (AR1) covariance structure. Once again, the best fitting model was identified by considering AIC and

likelihood ratio test. In all the three models, the intercept and the slope were allowed to vary within individuals.

2.6.2 Results

Table 14 shows AIC, -2LL and results of likelihood ratio tests for tested models for each of the 15 dimensions of QoL. ICC for Model 1 is reported as well. As reported, all ICC were above .25 and ranged from .26 to .65. These results attested that it was necessary to perform longitudinal analysis with repeated measure mixed models for all the 15 considered dimensions of QoL.

Table 14. ICC, AIC, -2LL and results of likelihood ratio tests for tested models (underlined the best fitting model among M1, M2, and M3; in italics, the best fitting model among M4, M5 and M6).

QoL	Model	ICC	AIC	-2LL	#EP	Comparison	Δ-2LL	Δdf	p
GHS	M1	.50	4461.49	4455.49	3	-	-	-	-
	M2	-	4407.33	4395.33	6	M1-M2	60.16	3	***
	M3	-	4399.45	4385.45	7	M2-M3	9.88	1	**
	M4	-	4282.58	4232.58	25	-	-	-	-
	M5	-	4303.05	4269.05	17	M4-M5	36.47	8	***
	M6	-	4276.52	4242.52	17	M4-M6	9.94	8	n.s.
PF	M1	.60	4464.18	4458.18	3	-	-	-	-
	M2	-	4445.56	4433.56	6	M1-M2	24.63	3	***
	M3	-	4420.28	4406.28	7	M2-M3	27.28	1	***
	M4	-	4225.07	4175.07	25	-	-	-	-
	M5	-	4242.02	4208.02	17	M4-M5	32.95	8	***
	M6	-	4253.14	4219.14	17	M4-M6	44.07	8	***
RF	M1	.54	4867.23	4861.23	3	-	-	-	-
	M2	-	4831.91	4819.91	6	M1-M2	41.33	3	***
	M3	-	4810.66	4796.66	7	M2-M3	23.25	1	***
	M4	-	4604.95	4554.95	25	-	-	-	-
	M5	-	4614.12	4580.12	17	M4-M5	25.17	8	**
	M6	-	4621.59	4587.59	17	M4-M6	32.64	8	***
EF	M1	.53	4422.01	4416.01	3	-	-	-	-
	M2	-	4386.90	4374.90	6	M1-M2	41.12	3	***
	M3	-	4387.88	4373.88	7	M2-M3	1.02	1	n.s.
	M4	-	4138.71	4098.71	20	-	-	-	-
	M5	-	4155.16	4131.16	12	M4-M5	32.45	8	***
	M6	-	4135.03	4111.03	12	M4-M6	12.32	8	n.s.

CF	M1	.65	4274.46	4268.46	3	-	-	-	-
	M2	-	4250.06	4238.06	6	M1-M2	30.40	3	***
	M3	-	4252.01	4238.01	7	M2-M3	0.05	1	n.s.
	M4	-	*4074.94*	*4034.94*	*20*	-	-	-	-
	M5	-	4091.37	4067.37	12	M4-M5	32.43	8	***
	M6	-	4090.10	4066.10	12	M4-M6	31.16	8	***
SF	M1	.52	4495.40	4489.40	3	-	-	-	-
	M2	-	4482.41	4470.41	6	M1-M2	18.99	3	***
	M3	-	4481.66	4467.66	7	M2-M3	2.74	1	n.s.
	M4	-	4376.62	4336.62	20	-	-	-	-
	M5	-	*4376.09*	*4352.09*	*12*	*M4-M5*	*15.48*	*8*	*n.s.*
	M6	-	4386.86	4362.86	12	M4-M6	26.24	8	**
FA	M1	.61	4533.00	4527.00	3	-	-	-	-
	M2	-	4500.74	4488.74	6	M1-M2	38.26	3	***
	M3	-	4482.64	4468.64	7	M2-M3	20.10	1	***
	M4	-	4268.79	4218.79	25	-	-	-	-
	M5	-	*4259.61*	*4225.61*	*17*	*M4-M5*	*6.82*	*8*	*n.s.*
	M6	-	4287.78	4253.78	17	M4-M6	34.99	8	**
NV	M1	.43	4271.99	4265.99	3	-	-	-	-
	M2	-	4235.73	4223.73	6	M1-M2	42.27	3	***
	M3	-	4233.48	4219.48	7	M2-M3	4.25	1	*
	M4	-	*4065.67*	*4015.67*	*25*	-	-	-	-
	M5	-	4134.39	4100.40	17	M4-M5	84.72	8	***
	M6	-	4122.28	4088.28	17	M4-M6	72.60	8	***
PA	M1	.54	4570.56	4564.56	3	-	-	-	-
	M2	-	4530.85	4518.85	6	M1-M2	45.71	3	***

	M3	-	4523.99	4509.99	7	M2-M3	8.86	1	**
	M4	-	*4159.21*	*4109.21*	*25*	-	-	-	-
	M5	-	4186.29	4152.29	17	M4-M5	43.07	8	***
	M6	-	4193.91	4159.91	17	M4-M6	50.70	8	***
DY	M1	.38	4987.10	4981.10	3	-	-	-	-
	M2	-	4980.15	4968.15	6	M1-M2	12.95	3	**
	M3	-	4976.78	4962.78	7	M2-M3	5.37	1	*
	M4	-	4789.35	4739.35	25	-	-	-	-
	M5	-	*4780.63*	*4746.63*	*17*	*M4-M5*	*7.28*	*8*	*n.s.*
	M6	-	4792.89	4758.89	17	M4-M6	19.54	8	**
IN	M1	.55	5041.78	5035.78	3	-	-	-	-
	M2	-	5024.71	5012.71	6	M1-M2	23.07	3	***
	M3	-	5013.63	4999.63	7	M2-M3	13.08	1	***
	M4	-	4832.47	4782.47	25	-	-	-	-
	M5	-	4841.44	4807.44	17	M4-M5	24.97	8	**
	M6	-	*4831.96*	*4797.96*	*17*	*M4-M6*	*15.48*	*8*	*n.s.*
AS	M1	.46	4996.77	4990.77	3	-	-	-	-
	M2	-	4934.42	4922.42	6	M1-M2	68.35	3	***
	M3	-	4923.87	4909.87	7	M2-M3	12.55	1	***
	M4	-	*4727.52*	*4677.52*	*25*	-	-	-	-
	M5	-	4764.70	4730.70	17	M4-M5	53.17	8	***
	M6	-	4746.70	4712.70	17	M4-M6	35.18	8	***
CO	M1	.48	4848.39	4842.39	3	-	-	-	-
	M2	-	4799.54	4787.54	6	M1-M2	54.85	3	***
	M3	-	4793.15	4779.15	7	M2-M3	8.39	1	***
	M4	-	*4675.50*	*4625.50*	*25*	-	-	-	-
	M5	-	4716.71	4682.71	17	M4-M5	57.21	8	***

		ICC	AIC	-2LL	#EP		Δ-2LL	Δdf	
	M6	-	4702.85	4668.85	17	M4-M6	43.35	8	***
DI	M1	.26	4333.62	4327.62	3	-	-	-	-
	M2	-	4313.64	4301.64	6	M1-M2	25.97	3	***
	M3	-	4315.12	4301.12	7	M2-M3	0.52	1	n.s.
	M4	-	*4260.42*	*4220.42*	*20*	-	-	-	-
	M5	-	4273.76	4249.76	12	M4-M5	22.17	8	***
	M6	-	4261.01	4237.01	12	M4-M6	9.42	8	*
FD	M1	.56	4614.05	4608.05	3	-	-	-	-
	M2	-	4610.34	4598.34	6	M1-M2	9.71	3	*
	M3	-	4612.34	4598.34	7	M2-M3	0.00	1	n.s.
	M4	-	*4472.48*	*4432.48*	*20*	-	-	-	-
	M5	-	4488.43	4464.43	12	M4-M5	31.95	8	***
	M6	-	4514.41	4490.41	12	M4-M6	57.93	8	***

Note: GHS = Global health status; PF = Physical functioning; RL = Role functioning; EF = Emotional functioning; CF = Cognitive functioning; SF = Social functioning; FA = Fatigue; NV = Nausea and vomiting; PA = Pain; DY = Dyspnoea; IN = Insomnia; AS = Appetite loss; CO =Constipation; DI = Diarrhoea; FD = Financial difficulties; ICC = Intraclass correlation; AIC = Akaike Information Criterion; -2LL = -2log likelihood; #EP = Number of estimated parameters; Δ-2LL = Differences in -2log likelihood between compared models; Δdf = Differences in number of estimated parameters/degrees of freedom

Global Health Status

The best fit of Model 3 attested that there were significant between-subject variations in the initial level of global health status and linear and quadratic trajectories over time. Thus, this model was retained in subsequent analyses to test whether pre-surgery global health status, age, type of surgery, and perioperative complications influenced initial QoL status at t1, linear growth rate, and quadratic change and to compare the three error covariance structures. Model 6 with AR1 covariance structure showed the best fit. Table 15 reports the final model with fixed effects for all the 15 dimensions of QoL. As shown, the initial level of global health status at t1 was 60.40 (S.E.=2.05; p<.001) and it increased linearly over time (B=

2.07; S.E. = 0.71; p < .01). However, the rate of quadratic change was not significant (B = -0.10; S.E. = 0.06; n.s.). Patients with higher level of pre-surgery global health status showed higher subsequent level at t1 (B = 0.13; S.E. = 0.19; p < .05). As shown in Figure 10A, patients with higher level of pre-surgery global health status reported a positive linear trend (B=0.04; S.E.= 0.03; p< .05) indicating that their GHS increase more over time, and a negative quadratic rate of change indicating that their rate of growth decelerated more over time (B = -0.01; S.E. = 0.01; p < .05). On the contrary, the rate of quadratic change was negative for patients experiencing perioperative complications (B = -0.20; S.E. = 0.09; p < .05) indicating that their increasing effect gradually diminished more over time (Figure 10B)

Table 15. Fixed effects for all the 15 dimensions of QoL.

	GHS	PF	RF	EF	CF	SF	FA	NV
Intercept	60.40 (2.05) ***	77.05 (1.78) ***	71.85 (2.54) ***	76.18 (2.00) ***	88.28 (1.51) ***	82.49 (2.01) ***	33.08 (2.22) ***	8.93 (1.47) ***
Time	2.07 (0.71) **	2.36 (0.53) ***	3.10 (0.79) ***	0.69 (0.27) *	-0.34 (0.19) n.s.	0.74 (0.22) **	-2.56 (0.73) **	-1.18 (0.41) **
TimeQ	-0.10 (0.06) n.s.	-0.17 (0.05) ***	-0.20 (0.07) **	-	-	-	0.15 (0.07) *	0.07 (0.04) n.s.
T0	0.13 (0.07) *	0.52 (0.10) ***	0.41 (0.10) ***	0.48 (0.07) ***	0.50 (0.06) ***	0.35 (0.09) ***	0.52 (0.08) ***	0.12 (0.16) n.s.
TS at t0	4.69 (3.07) n.s.	4.66 (2.70) n.s.	7.04 (3.81) n.s.	3.80 (2.97) n.s.	3.37 (2.25) n.s.	5.40 (2.95) n.s.	-0.37 (3.36) n.s.	-4.23 (2.22) n.s.
PC	-4.64 (3.08) n.s.	-6.30 (2.73) *	-7.91 (2.87) *	-1.79 (2.98) n.s.	-1.00 (2.24) n.s.	-2.58 (3.00) n.s.	8.01 (3.35) *	0.11 (2.24) n.s.
Age	-0.13 (0.19) n.s.	-0.14 (0.17) n.s	0.32 (0.23) n.s.	-0.13 (0.18) n.s.	-0.16 (0.14) n.s.	0.28 (0.18) n.s.	0.17 (0.20) n.s.	-0.10 (0.13) n.s.
Time*t0 QoL	0.05 (0.02) *	0.01 (0.03) n.s.	-0.04 (0.03) n.s.	-0.02 (0.01) **	-0.01 (0.01) n.s.	-0.02 (0.01) n.s.	-0.05 (0.03) n.s.	-0.07 (0.04) n.s.
Time*TS	-1.17 (1.03) n.s.	-1.94 (0.80) *	-1.78 (1.18) n.s.	-0.49 (0.40) n.s.	0.11 (0.28) n.s.	-0.08 (0.33) n.s.	0.35 (1.09) n.s.	0.55 (0.62) n.s.
Time*PC	1.76 (1.05) n.s.	1.49 (0.83) n.s.	3.27 (1.21) **	-0.67 (0.41) n.s.	0.00 (0.29) n.s.	-0.40 (0.34) n.s.	-2.01 (1.10) n.s.	-0.33 (0.63) n.s.
Time*Age	-0.04 (0.07) n.s.	0.15 (0.05) n.s.	-0.09 (0.07) n.s.	0.02 (0.02) n.s.	0.01 (0.02) n.s.	-0.02 (0.02) n.s.	0.01 (0.07) n.s.	-0.02 (0.04) n.s.
TimeQ*t0 QoL	-0.01 (0.00) *	-0.00 (0.00) n.s.	0.00 (0.00) n.s.	-	-	-	0.00 (0.00) n.s.	0.01 (0.00) n.s.
TimeQ*TS	0.11 (0.09) n.s.	0.18 (0.07) *	0.19 (0.10) n.s.	-	-	-	-0.06 (0.10) n.s.	-0.04 (0.06) n.s.
TimeQ*PC	-0.20 (0.09) *	-0.14 (0.70) n.s.	-0.32 (0.11) **	-	-	-	0.22 (0.10) *	0.05 (0.06) n.s.
TimeQ*Age	0.01 (0.01) n.s.	0.00 (0.00) n.s.	0.01 (0.01) n.s	-	-	-	-0.00 (0.00) n.s.	0.00 (0.00) n.s.

	PA	DY	IN	AS	CO	DI	FD
Intercept	23.60 (2.39) ***	29.95 (2.37) ***	28.11 (2.76) ***	26.63 (3.07) ***	27.73 (3.15) ***	6.73 (1.57) ***	12.57 (2.03) ***
Time	-1.58 (0.79) *	-0.77 (0.97) n.s.	-3.73 (0.93) ***	-4.39 (0.88) ***	-2.89 (0.98) **	-0.11 (0.24) n.s.	-0.03 (0.25) n.s.
TimeQ	0.06 (0.06) n.s.	0.03 (0.09) n.s.	0.24 (0.08) **	0.24 (0.08) **	0.15 (0.08) n.s.	-	-
T0	0.47 (0.11) ***	0.42 (0.09) ***	0.28 (0.08) ***	.23 (0.13) n.s.	0.56 (0.09) ***	0.37 (0.08) ***	0.42 (0.06) ***
TS at t0	-1.35 (3.61) n.s.	-4.04 (2.52) n.s.	-5.01 (4.11) n.s.	12.17 (4.56) **	-6.41 (4.69) n.s.	-2.36 (2.33) n.s.	-2.4 (2.98) n.s.
PC	4.84 (3.71) n.s.	9.41 (3.59) **	-0.87 (4.23) n.s.	-4.14 (4.65) n.s.	2.83 (4.70) n.s.	-2.88 (2.35) n.s.	0.69 (3.00) n.s.
Age	-0.34 (0.22) n.s.	-0.21 (0.22) n.s.	-0.13 (0.25) n.s.	0.26 (0.28) n.s.	0.33 (.029) n.s.	-0.22 (0.14) n.s.	-0.40 (0.18) *
Time*t0 QoL	-0.06 (0.03) n.s.	-0.00 (0.04) n.s.	-0.01 (0.03) n.s.	-0.05 (0.04) n.s.	-0.08 (0.03) **	-0.02 (0.1) *	0.00 (0.01) n.s.
Time*TS	-1.45 (1.61) n.s.	0.22 (1.42) n.s.	3.37 (1.38) *	3.01 (1.31) *	1.00 (1.42) n.s.	0.14 (0.35) n.s.	-0.21 (0.37) n.s.
Time*PC	0.37 (1.22) n.s.	-4.06 (1.50) **	0.38 (1.42) n.s.	0.78 (1.34) n.s.	-0.53 (1.44) n.s.	0.35 (0.35) n.s.	0.88 (0.37) *
Time*Age	0.02 (0.07) n.s.	0.09 (0.09) n.s.	-0.10 (0.09) n.s.	-0.07 (0.08) n.s.	0.07 (0.09) n.s.	0.04 (0.02) n.s.	0.04 (003) n.s.
TimeQ*t0 QoL	0.01 (0.00) n.s.	-0.00 (0.00) n.s.	0.00 (0.00) n.s.	0.00 (0.00) n.s.	0.01 (0.00) **	-	-
TimeQ*TS	0.14 (0.10) n.s.	-0.08 (0.13) n.s.	-0.24 (0.12) *	-0.20 (0.11) n.s.	-0.1 (0.12) n.s.	-	-
TimeQ*PC	-0.03 (0.10) n.s.	0.37 (0.13) **	0.09 (0.12) n.s.	0.07 (0.12) n.s.	0.02 (0.12) n.s.	-	-
TimeQ*Age	0.00 (0.0) n.s.	-0.01 (0.01) n.s.	0.01 (0.01) n.s.	0.01 (0.01) n.s.	-0.01 (0.01) n.s.	-	-

Note: GHS = Global health status; PF = Physical functioning; RL = Role functioning; EF = Emotional functioning; CF = Cognitive functioning; SF = Social functioning; FA = Fatigue; NV = Nausea and vomiting; PA = Pain; DY = Dyspnoea; IN = Insomnia; AS = Appetite loss; CO =Constipation; DI = Diarrhoea; FD = Financial difficulties; Time = Linear rate of growth; TimeQ = Quadratic rate of growth; T0 = pre-surgery subscales score; TS = type of surgery at t0; PC = Perioperative complications.

Physical Functioning

The best fit of Model 3 attested that there were significant between-subject variations in the initial level of physical functioning, and linear and quadratic trajectories over time. Model 4 with UN covariance structure showed the best fit. As shown, the initial level of physical functioning at t1 was 77.05 (S.E. = 1.78; $p < .001$), increased linearly (B = 2.36; S.E. = 0.53; $p < .001$) and decelerated over time (B = -0.17; S.E. = 0.05; $p < .001$). Patients with higher pre-surgery physical functioning level (B = 0.52; S.E. = 0.10; $p < .001$) and without perioperative complications (B = -6.30; S.E. = 2.73; $p < .01$) showed higher subsequent level at t1. Type of surgery moderated rates of both linear and quadratic change. Specifically, as shown in Figure 10C, patients undergoing robot-assisted surgery, compared to patients undergoing traditional surgery, reported a slower linear increase (B = -1.94, S.E. = 0.80; $p < .05$) but the positive quadratic effect (B = 0.18; S.E. = 0.07; $p < .05$) indicated that their rate of change decelerated less over time.

Role Functioning

The best fit of Model 3 attested that there were significant between-subject variations in the initial level of role functioning, and linear and quadratic trajectories over time. Model 4 with UN covariance structure showed the best fit. A t1, the level of role functioning was 71.85 (S.E. = 2.54; $p < .001$), increased linearly (B = 3.10; S.E. = 0.79; $p < .001$) and decelerated over time (B = -0.20; S.E. = 0.07; $p < .01$). Patients with higher pre-surgery role functioning level (B = 0.41; S.E. = 0.10; $p < .001$) and without perioperative complications (B = -7.91; S.E. = 3.87; $p < .01$) showed higher level of role functioning at t1. The experiencing of perioperative complications moderated rates of both linear and quadratic change of role functioning. Specifically, as shown in Figure 10D, patients with perioperative complications, compared to patients without complications, reported a faster increase (B = 3.27; S.E. = 1.21; $p < .001$) but this increasing effect gradually diminished more (B = -0.32; S.E. = 0.11; $p < .01$) over time.

Emotional Functioning

The best fit of Model 2 attested that there were significant between-subject variations in the initial level of emotional functioning and linear trajectories over time. Model 6 with AR1 covariance structure showed the best fit. Emotional functioning at t1 was 76.18 (S.E. = 2.00; $p < .001$) and increased linearly over time (B = 0.69; S.E. = 0.27; $p < .01$). Patients with higher pre-surgery emotional functioning level (B = 0.48; S.E. = 0.10; $p < .001$) showed higher level at t1. Moreover, level of pre-surgery emotional functioning moderated rates of linear change of emotional functioning. Specifically, patients with higher pre-surgery level reported a slower increase of emotional functioning over time (B = -0.02; S.E. = 0.01; $p < .01$).

Cognitive Functioning

The best fit of Model 2 attested that there were significant between-subject variations in the initial level of emotional functioning and linear trajectories over time. Model 4 with UN covariance structure showed the best fit. At t1, cognitive functioning was 88.28 (S.E. = 1.51 $p < .001$) and did not linearly increase over time (B = -0.34; S.E. = 0.19; n.s.). Patients with higher pre-surgery cognitive functioning level showed higher level at t1 (B = 0.50; S.E. = 0.06; $p < .001$). Any of the sociodemographic or clinical variables influenced linear rate of change over time.

Social Functioning

The best fit of Model 2 attested that there were significant between-subject variations in the initial level of social functioning and linear trajectories over time. Model 5 with CS covariance structure showed the best fit. Social functioning at t1 was 82.49 (S.E. = 2.01; $p < .001$) and increased linearly over time (B = 0.74; S.E. = 0.22; $p < .01$). Patients with higher pre-surgery social functioning level showed higher level of social functioning at t1 (B = 0.35; S.E. = 0.09; $p < .001$). Any of the sociodemographic or clinical variables influenced the linear rate of change of social functioning over time.

Fatigue

The best fit of Model 3 attested that there were significant between-subject variations in the initial level of fatigue, and linear and quadratic trajectories over time. Model 5 with CS covariance structure showed the best fit. A t1, the level of fatigue was 33.08 (S.E. = 2.22; p < .001), decreased linearly (B = -2.56; S.E. = 0.73; p < .01) but decelerated over time (B = 0.15; S.E. = 0.07; p < .05). Patients with higher level of pre-surgery fatigue (B = 0.52; S.E. = 0.08; p < .001) and with perioperative complications (B = 8.01; S.E. = 3.35; p < .05) showed higher level of fatigue at t1. The experiencing of perioperative complications moderated the quadratic rate of growth of fatigue over time. Specifically, as shown in Figure 10E, patients with perioperative complications, compared to patients without complications, reported a higher deceleration of decreasing rate of fatigue over time (B = 0.22; S.E. = 0.10; p < .05).

Nausea and Vomiting

The best fit of Model 3 attested that there were significant between-subject variations in the initial level of nausea and vomiting and linear and quadratic trajectories over time. Model 4 with UN covariance structure showed the best fit. After the inclusion of predictors, the level of nausea and vomiting at t1 was 8.938 (S.E. = 1.47; p < .001) and decreased linearly over time (B = -1.18; S.E. = 0.41; p < .01). Any of the sociodemographic or clinical variables influenced initial status of nausea and vomiting, neither linear and quadratic rate of change of fatigue over time.

Pain

The best fit of Model 3 attested that there were significant between-subject variations in the initial level of pain and linear and quadratic trajectories over time. Model 4 with UN covariance structure showed the best fit. Pain at t1 was 23.60 (S.E. = 2.39; p < .001) and decreased linearly over time (B = -1.58; S.E. = 0.79; p < .05). Patients with higher pre-surgery pain showed higher level of this QoL dimension at t1 (B=0.47; S.E.=0.11; p<.001).

Dyspnoea

The best fit of Model 3 attested that there were significant between-subject variations in the initial level of dyspnoea, and linear and quadratic trajectories over time. Model 5 with CS covariance structure showed the best fit. A t1, the level of dyspnea was 29.95 (S.E. = 2.37; p < .001) but it did not increase linearly (B = -0.77; S.E. = 2.37; n.s.) neither accelerated over time (B = -0.77; S.E. = 0.98; n.s.). Patients with higher level of pre-surgery dyspnea (B = 0.42; S.E. = 0.09; p < .001) and with perioperative complications (B = 9.41; S.E. = 3.59; p < .01) showed higher level of this QoL dimension at t1. The experiencing of perioperative complications moderated rates of both linear and quadratic change of dyspnoea. Specifically, as shown in Figure 10F, patients with perioperative complications, compared to patients without complications, reported a steeper decrease (B = -5.06; S.E. = 1.47; p < .01) but a faster deceleration of decreasing effect over time (B = .37; S.E. = 0.13; p < .01).

Insomnia

The best fit of Model 3 attested that there were significant between-subject variations in the initial level of insomnia, and linear and quadratic trajectories over time. Model 6 with AR1 covariance structure showed the best fit. As shown, the initial level of insomnia at t1 was 28.11 (S.E. = 2.76; p < .001), decreased linearly (B = -3.73; S.E. = 0.93; p < .001) and decelerated over time (B = 0.24; S.E. = 0.08; p < .01). Patients with higher level of pre-surgery insomnia showed higher level at t1 (B = 0.28; S.E. = 0.08; p < .001). Type of surgery moderated rates of both linear and quadratic change. Specifically, as shown in Figure 10G, patients undergoing robot-assisted surgery, compared to patients undergoing traditional surgery, reported a slower linear change (B =3.37; S.E. = 1.38; p < .05) but a slower deceleration of decreasing effect over time (B = -0.24; S.E. = 0.12; p < .05).

Appetite Loss

The best fit of Model 3 attested that there were significant between-subject variations in the initial level of appetite loss, and linear and quadratic trajectories over time. Model 4 with UN covariance structure showed the best fit. Appetite loss at t1 was 26.63 (S.E. = 3.07; p <

.001), decreased linearly (B = -4.39; S.E. = 0.88; p < .001) and decelerated over time (B = 0.24; S.E. = 0.08; p < .01). Patients undergoing robot-assisted surgery showed lower level of appetite loss at t1 (B = 12.17; S.E. = 4.56; p < .01). Moreover, type of surgery moderated rates of linear change of appetite loss over time. Specifically, as shown in Figure 10H, patients undergoing robot-assisted surgery, compared to patients undergoing traditional surgery, reported a slower linear decrease over time (B =3.01; S.E. = 1.31; p < .05).

Constipation

The best fit of Model 3 attested that there were significant between-subject variations in the initial level of constipation, and linear and quadratic trajectories over time. Model 4 with UN covariance structure showed the best fit. At t1, the initial level of constipation was 27.73 (S.E. = 3.15; p < .001) and it decreased linearly over time (B = -2.89; S.E. = 0.97; p < .01). Patients with higher level of pre-surgery constipation showed higher subsequent level at t1 (B = 0.56; S.E. = 0.09; p < .001). As shown in Figure 10I, the decreasing effect was faster for patients with higher level of pre-surgery constipation (B = -0.08; S.E. = 0.03; p < .01) but they showed less acceleration of decreasing effect over time (B = 0.01; S.E. = 0.00; p < .01).

Diarrhea

The best fit of Model 2 attested that there were significant between-subject variations in the initial level of diarrhea and linear trajectories over time. Model 4 with UN covariance structure showed the best fit. Diarrhea t1 was 6.73 (S.E. = 1.57; p < .001) but, after the inclusion of sociodemographic and clinical predictors, it did not linearly change over time (B = -0.11; S.E. = 0.24; n.s.). Patients with higher level of pre-surgery diarrhea showed higher level at t1 (B = 0.37; S.E. = 0.08; p < .001) and reported a faster decrease over time (B = -0.02; S.E. = 0.01; p < 0.5).

Financial Difficulties

The best fit of Model 2 attested that there were significant between-subject variations in the initial level of financial difficulties and linear trajectories over time. Model 4 with UN covariance structure showed the best fit. At t1, financial difficulties score was 12.57 (S.E. = 2.03; $p < .001$) but, after the inclusion of sociodemographic and clinical predictors, it did not linearly change over time (B = -0.04; S.E. = 0.25; n.s.). Patients with higher level of pre-surgery financial difficulties (B = 0.42; S.E. = 0.06; $p < .001$) and younger patients (B = -0.40; S.E. = 0.18; $p < .05$) reported higher level at t1. Moreover, patients with perioperative complications reported a faster increase of financial difficulties over time than patients without this kind of difficulties (B = 0.88; S.E. = 0.37; $p < .05$).

Figure 10: Longitudinal trends of QOL domains
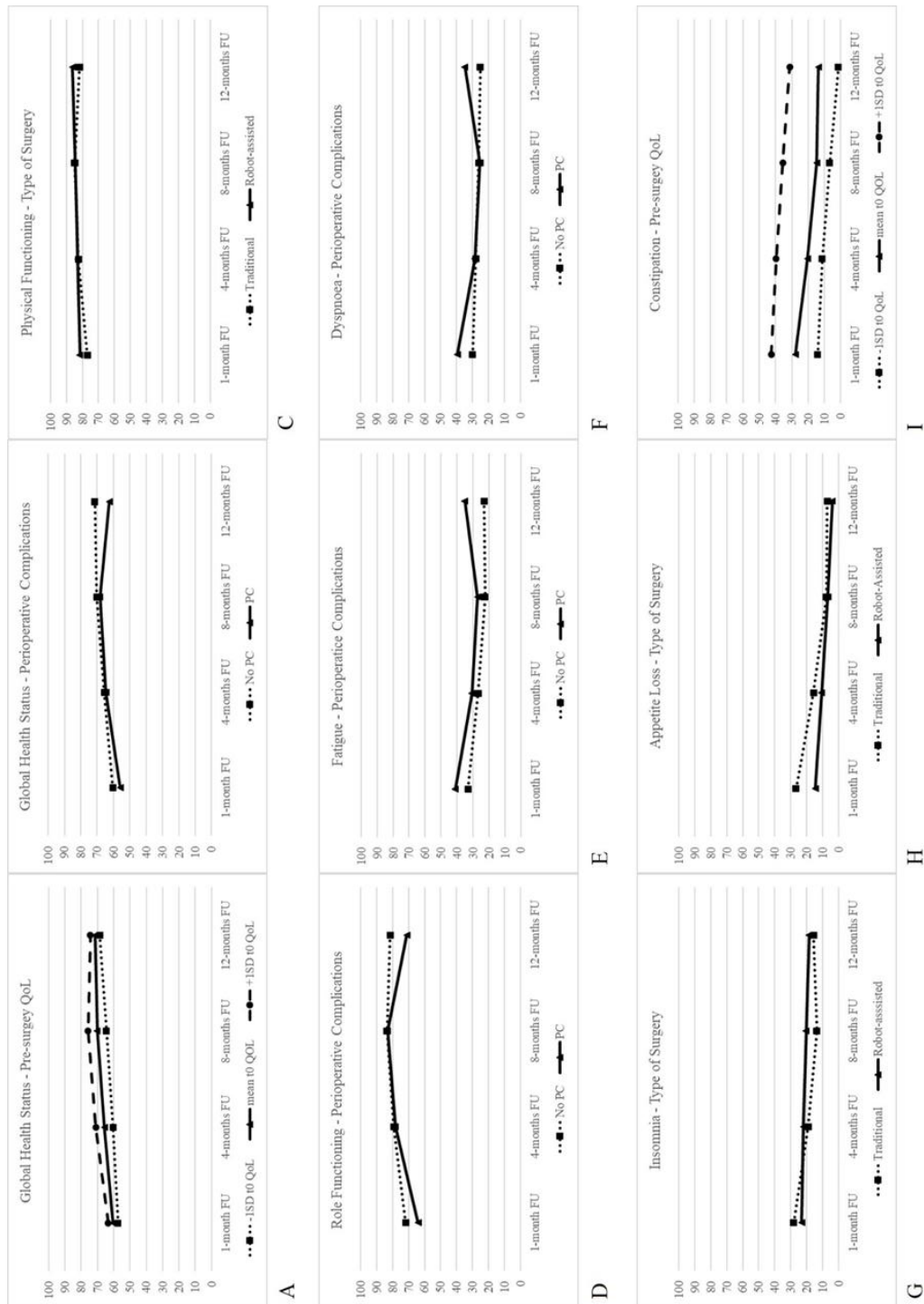
2.6.3 Discussion

The present study identified one-year trends of patients' QoL after pulmonary lobectomy for NSCLC and investigated whether clinical and sociodemographic variables may predict these trends. The individual change over time of the fifteen dimensions of the EORTC QLQ-C30 and the effects of pre-surgery scores of QoL dimensions, type of surgery, perioperative

complications, and age on patients' QoL after surgery were studied with the individual growth curve (IGCs) models.

According to other previous studies[177], our results showed that patients had a good recovery after lobectomy. This is attested by an overall decrease of symptoms and an increase of health and functioning over time. However, levels of QoL at pre-surgery, type of surgery, perioperative complications, and patient's age generally affected the post-surgery initial status of QoL as well as its linear and quadratic trends over time. This overall recovery in QoL is quite clear by looking at the results concerning the GHS. Specifically, patients' health increased linearly over time. Pre-surgery GHS significantly affected its trend after lobectomy: lung cancer patients with high levels of pre-surgery GHS had better score at t1 and better one-year recovery, even if their beneficial trend tended to slow down over time. Also, patients experiencing perioperative complications, compared with people with no complications, reported a greater deceleration of the recovery rate over time suggesting that this kind of patients are likely to experience a late relapse of global health.

Referring to the European reference values for the quality of life questionnaire EORTC QLQ-C30 (2008)[178], one month after surgery (t1) patients globally reported high physical, role, emotional, cognitive and social functioning score rates, varying from 71.85 (role function) to 88.28 (cognitive function). Except for cognitive functioning (presenting high levels at all time periods), all the other functioning subscales linearly increased over time, showing a fast and good recovery after surgery. Only the recovery trend of physical and role functioning significantly decelerated over time: the linear improvement of both functions was faster in the first months after surgery and tended to become slower as time went on. Emotional, cognitive, and social subscales constantly increased over time indicating that patients are likely to have a good psychosocial recovery after surgery. A recent systematic review (2015) on QoL after lung cancer resection, showed physical functioning is the most affected dimension in patients with NSCLC, but all the EORTC QLQ-C30 subscales generally recover in 3-12 months after surgery[177].

Pre-surgery levels significantly impacted all functioning subscales at t1: patients with high levels of physical, role, emotional, cognitive, and social functions before surgery showed higher levels even one month after surgery. Moreover, patients with higher pre-surgery emotional functioning had a slower improvement of this QoL over time. Among the other aspects that may affect patients' functions, type of surgery significantly impacted only on the linear and quadratic trend of physical functioning over time. Specifically, compared to patients undergoing robot-assisted surgery, people undergoing traditional surgery displayed a faster linear improvement in physical functioning after lobectomy, but this recovery remained less stable over time for patients undergoing traditional surgery. Balduyck et al. (2007)[179], analyzing patients undergoing traditional or robotic-assisted surgery, demonstrated that patients undergoing traditional lobectomy had worse effects on physical functioning and pain over one-year. Our results attested that patients' functioning may be affected also by perioperative complications as well. Specifically, lung cancer patients with perioperative complications had lower scores in physical and role functions thirty days after surgery but a faster recovery from role functioning impairment. However, the speed of recovery from emotional problems tended to slow down more at later time (or become even worse) for patients experiencing complications.

The symptom subscales trends were also investigated. Patients' reported symptoms at t1 were in line with the reference scores values[178] of lung cancer. Only dyspnoea and constipation symptoms were lower than their reference score means: 30 days after surgery patients reported dyspnoea of 29.95 and constipation of 27.73, whereas the average mean are 42.7 and 15.0, respectively. Since higher rates indicate worse symptoms, lung cancer patients undergoing lobectomy in our study had fewer problems of dyspnoea and more constipation than expected. This could be explained by the continuous use of post-operative pain killers even after 30 days conditioning a better pulmonary function due to less pain but increasing constipation. The one-year trend linearly decreased for fatigue, pain, insomnia, appetite loss, and constipation, suggesting a recovery from symptoms over time. However,

the speed of recovery gradually slowed down for fatigue and appetite loss as time from surgery went on, prolonging patients' tiredness and inappetence.

Pre-surgery levels significantly impacted fatigue, pain, dyspnea, insomnia, constipation, diarrhea, and financial difficulties at t1: patients with high levels of these symptoms before surgery showed higher problems even at t1. Moreover, patients with higher pre-surgery levels of constipation and diarrhea had a faster decrease in these symptoms over time, but the first one showed a slower recovery in the last months of the one-year trend. The type of surgery significantly impacted insomnia and appetite loss rates at t1 and over time: patients undergoing robot-assisted surgery had low scores at t1 but a slower improvement after lobectomy in these symptoms than patients undergoing traditional surgery. This slow improvement is probably due to the favorable initial condition: patients undergoing robot-assisted surgery had fewer symptoms at t1, and they may not further improve over time since they already had high scores thirty days after surgery. However, the significant negative quadratic change of insomnia showed that it remained more stable over time for patients undergoing robot-assisted lobectomy, suggesting that patients undergoing traditional surgery were more likely to experience a worsening of sleep problems at later time. Perioperative complications significantly affected the t1 scores of dyspnoea and fatigue: lung cancer patients with perioperative complications had higher levels of dyspnoea and fatigue thirty days after surgery. Moreover, complications affected the recovery of dyspnoea and financial difficulties over time: patients with no complications had a faster increase of dyspnoea symptom and a slower increase in financial difficulties and spent less money. Finally, the quadratic change of dyspnoea and fatigue were impacted by perioperative complications, showing a greater slowdown of the recovery for patients with complications. Age significantly impacted only on financial difficulties: younger patients had greater financial problems thirty days after surgery than older people.

The obtained results identify different one-year trends of lung cancer patients' QoL after lobectomy. All sub-dimensions had a specific recovery: functioning subscales improved

over time, while most of the symptoms became less severe over the care process. Perioperative complications, type of surgery, pre-surgery status and age significantly affected these trends, thus becoming predictors of patients' QoL. In fact, in this paper it was often demonstrated that pre-surgery QoL rates often predicted post-surgery status and trends, while the type of surgery, age, and perioperative complications often affect patients' well-being and recovery. Therefore, the measurement of pre- and post-surgery QoL and its clinical and sociodemographic covariables would be necessary to better investigate patients' care process and implement personalized medicine in lung cancer hospital divisions. A patient-centered approach would be important to develop preventive programs, analyze both psychological and medical outcomes that could affect patient's recovery, and improve patient empowerment[180,181].

Limitations

Current results may be considered in light of some main limitations. Specifically, because of sample size, it was not possible to identify different typologies of patients following different longitudinal trajectories of QoL: 176 patients with lung cancer were not enough to distinguish different trend of recovery. This study shows the average one-year trend, but it did not identify different classes of patients with different recovery after surgery. Future studies should be conducted on a larger sample in order to perform other statistical analyses with a typological approach that can better describe patients' recovery. It would be also important to collect data on the effects of other psychological aspects that may significantly impact the trend of patients' QoL. For example, illness perception, resilience, coping, and self-efficacy are only some of the important aspects that should be measured over the care cycle and may modify patients' recovery after surgery[182–184]. Future studies are needed to better identify covariables that may impact on lung cancer patients' QoL and identify different trajectories of patients' recovery[185]. Moreover, measured outcomes were collected up to only one year after surgery: it would be important to extend the follow-ups, in order to better analyze patient's recovery of functions, which mostly lasts more than one

year after treatments. Lastly, since QoL is strictly associated with survivorship rates, it would be useful to conduct another project studying which QoL sub-dimensions may interact or affect patients' survivorship[162].

3. Conclusions

The VBHC paradigm aims at improving the health care process, collecting data from a psychological, clinical and economic perspective and improving the quality of care. This paradigm has been implemented in different health care organizations, even if combining countries' current health care systems and the VBHC model is still a challenge. In Italy, only two health care organizations are currently applying some aspects of the VBHC model. The European Institute of Oncology applied the VBHC framework to different medical divisions, implementing the VBM project. Clinical, psychological and economic data have been collected in prostate and lung cancer patients for two years. The VBM project aims at analysing principal and interaction effects between outcomes and costs investigating the associations among psychological, medical and economic aspects of patient's process of care, and studying if the psychological status may impact on costs, rehabilitation, drug consumption and medical examinations. The Psychoncology division focused on patients' well-being in order to identify trend of clinical and psychological status over time and predict this change with sociodemographic or medical variables. A person-oriented approach was used to analyze patients' recovery: one-year QoL trends in early stage of lung and prostate cancer patients undergoing surgery were identified, along with the sociodemographic and clinical factors that may impact and affect these trends. Patients' recovery after surgery was characterized by an overall decrease of symptoms and an increase of health and functioning over time. In lung cancer, levels of QoL at pre-surgery, type of surgery, perioperative complications, and patient's age generally affected post-surgery initial status of QoL as well as its linear and quadratic trends over time. On the contrary, due to a larger sample, different categories of prostate cancer patients characterized by different trend of clinical and psychological status over time were also identified: five and three classes were found for urinary incontinence and sexual dysfunction subscales, respectively. The membership to one of the identified classes may be affected by age, pre-surgical condition and BMI. However, all the predictors analysed so far were clinical or sociodemographic variables; psychological

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outcomes should be included to better understand the differences among patients' trajectories. Finding different categories of patients at risk may be important to develop personalized medical pathways and predictive models in value-based health care. Through the collection of clinical outcomes and costs, a predictive model of patients' recovery would be developed, allowing a more precise framework on patients' care pathway. Predictive models would improve medical decision-making, the choice of treatment, and patients' awareness about their care process: in this way, potential risks, QoL, and expected outcomes would be more predictable and better manageable. Even the patient would be more empowered, thus becoming an active decision-maker[106]. Starting from data collected on prostate and lung cancer patients, the second phase of the VBM project will be to implement and validate a personalized model able to predict the patient's care process. According to the sociodemographic and clinical characteristics, every patient will receive a personalised predictive model of his/her functional and psychological recovery after surgery. At the first medical consultation in the Urology Division at the IEO, prostate cancer patients candidate for RARP will receive a personalized predictive model that allow both patients and physicians to gather more information about treatments' risks and expected outcomes over time. To understand the effects of this innovative form of communication of clinical results, a qualitative analysis will be carried out by a psychologist who will verify the degree of patients' awareness about their clinical-functional risk profile. The semi-structured interview will be conducted after the creation and explanation of the "profile" and before the patient will undergo surgery; emotional and cognitive aspects related to the diagnosis and the expected recovery will be also investigated.

Another future direction would be to investigate patients' QoL and trajectories of recovery by differentiating for type of cancer. Until now, the process of care for single type of cancer has been analysed, but they have not yet been compared. Every cancer is characterized by specific drug consumption and side effects, different time for recovery, and costs; comparing

the trajectories among patients with lung and prostate cancer would allow to understand which factors may influence both processes of care.

Despite all the advancements in predicting patients' trajectories of recovery, the psychological dimension needs to be further investigated. Until now, QoL was the only measured psychological outcome in prostate and lung cancer patients, but several aspects of the predictive trajectories of patients' recovery were still unexplained. The obtained results emphasised the need to add other variables that may significantly affect patients' care pathway. Next studies referring to the VBM project will improve these aspects.

For this reason, the VBM project that would focus on breast cancer patients will implement specific modifications to the related research protocol: psychological variables that may affect the overall status of the patient will be included. Thereby, to further investigate which factors may moderate or mediate the psychological dimension of cancer patients, other psychological variables would be included in the VBM Breast Cancer research protocol.

3.1 The VBM project on breast cancer patients: a new challenge.

According to these research trajectories a new research protocol has been developed on breast cancer patients at European Institute of Oncology. The Value-Based Project in the Breast Unit (VBM-Breast Protocol) aims to implement VBHC model along the disease trajectory in breast cancer patients. In details, it is a concrete attempt to achieve a depth integration, validation and dissemination of the VBHC model in clinical practice for cancer disease in the Italian context. The VBM-Breast Protocol was developed after the conclusion of prostate and lung cancer studies and it has been nested in the same theoretical background. The high incidence of breast cancer (more than 2.1 million women in the world[41]) and the clinical, psycho-social and economic implications related to it, have stressed the importance of an integrative and comprehensive model able to explain the complexity of this condition. Furthermore, the studies on prostate and lung cancer patients showed that QoL deeply affects patients' recovery after surgery, underlining the importance of psychological aspects in cancer care. These results suggested the crucial role of psycho-social factors in defining

health status of cancer patients. More in details, evidence have reported the importance of specific psychological mechanisms such as : resilience, self-efficacy, optimism, and illness perception[186–189]. These variables may scale up the assessment of the QoL. For example, innovative relations have been found for resilience. In the context of cancer, resilience has been recently defined as dynamic "individual's protective attributes and/or personal characteristics, which are thought to be modifiable and to promote successful adaptation to cancer, including, among others, meaning and purpose in life, sense of coherence, optimism, positive emotions, self-esteem, self-efficacy, cognitive flexibility, coping, social support, and spirituality"[190]. Breast cancer women with low levels of resilience have a worse perception of their body image and more severe symptoms, thus impacting different HRQoL aspects[188]. Other studies showed that self-efficacy and optimism may affect patients' abilities to cope with cancer and improve psychological well-being: high levels of self-efficacy and dispositional optimism are associated with better QoL among breast cancer patients[191,192]. Lastly, illness perception is defined as "patients' cognitive, feelings, and emotions about symptoms they experience and their disease in general"; several scientific studies showed its relationship with breast cancer patients' QoL[193]. Since illness perception showed an high association with low levels of HRQoL, it would be important to better investigate its role as a possible mediator/moderator on QoL[187].

Within the VBM - Breast project these psychological variables were included in order to not only identify trend of patients' recovery over time variables, but also to analyze which psychological factors may mediate or moderate QoL outcomes over the care cycle. In order to disseminate the principles of VBHC model, the VBM-Breast project will be designed as a multicentre prospective longitudinal study, thus involving different Italian Hospitals. The Italian Hospital involved are the European Institute of Oncology, the Istituto Nazionale dei Tumori IRCCS, the ASST Papa Giovanni XXIII (Bergamo), the ASST dei 7 Laghi (Varese), the Fondazione Policlinico S. Matteo IRCCS (Pavia), and the ASST di Cremona. Based on

the number of patients undergoing breast cancer surgery per year, different sample size will be calculated. Table 16 shows the expected number of patients to be enrolled.

Table 16. Expected number of patients to be enrolled at each healthcare organizations

Hospital	*Expected number of patients*
European Institute of Oncology IRCCS	900
Istituto Nazionale dei Tumori IRCCS	300
ASST Papa Giovanni XXIII	150
ASST dei 7 Laghi	120
Fondazione Policlinico S. Matteo IRCCS	80
ASST di Cremona	80

For all the healthcare institutions, only patients 1) older than 18 years, 2) with primary breast cancer, and 3) undergoing mastectomy or quadrantectomy with or without reconstruction would be enrolled.

According to patients' follow-ups, data will be collected at different time points − at pre-surgery (t0), 1 (t1), 6 (t2), 12 (t3), and 24 (t4) months after surgery − through specific standardized questionnaires measuring the above-mentioned psychological variables.

The EORTC QLQ-C30 and the EORTC QLQ-BR-23, two self-report questionnaires composed of 30 and 23 items, respectively, will be used to measure QoL in breast cancer patients. The EORTC QLQ-C30 has already been described in the lung cancer section; on the contrary, the specific section BR-23 is used to assess specific symptoms related to the breast cancer condition. In fact, it is composed by five sub-scales assessing body image, sexual functioning, sexual enjoyment, future perspective, treatments' side effects, breast symptoms, arm symptoms and upset by hair loss[116,122,194].

Resilience will be measured through the Resilience Scale for Adult (RSA), a 33-items questionnaire with different sub-scales collecting inter- and intra-personal protective factors that may influence the patient's adjustment. More specifically, intra-personal subscales

investigate self-perception, planned future, social competence, and structured style. On the contrary, inter-personal subscales assess family cohesion and social resources[195,196].

Self-efficacy is a context-specific variable that will be assessed through the brief version of the Cancer Behavior Inventory (CBI-B), a 14 items survey with a 9-points Likert scale. The questionnaire investigated the ability to maintain independence and positive attitude, seeking and understanding medical information, coping and stress management, and the emotion regulation[197,198]. Dispositional optimism is a relatively stable psychological resource [199] assessed by the Life Orientation Test-Revised (LOT-R), a self-report questionnaire of 10 items with a 5-points Likert scale[135,200]. Finally, illness perception will be measured with the Brief Illness Perception Questionnaire (BIP-Q), a 9-items self-report scale that investigates cognitive and emotional representations of illness, and comprehension of illness[201].

A trained psychologist will meet patients at pre-surgery, giving them the inform consent and collecting psychological variables through the standardized questionnaires. During the follow-ups, data will be collected through a specific e-health platform called REDCup. Patients with low psychological well-being will be then contacted and their needs will be investigated.

Concluding, the VBM-Breast Protocol is a key opportunity and a pivotal challenge to try to confirm the results obtained in Study 1b on prostate cancer and Study 2b on lung cancer and to integrate the VBHC model in clinical practice for cancer care using a patient centered approach. This approach will permit to identify all psychological, social and economic unmet need of the cancer patients and try to respond them.

The implementation of this approach will improve decision-making in clinicians and patients pushing them to achieve a shared decision about treatments. Consequently, it guarantees the opportunity to better involve the cancer patients in their disease management, empowering them.

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Appendix

A1. Search strategy for the review on Italian hospitals applying the VBHC to medical practice

Search Engine:	Search String:	Hits	Relevant[a]	Included[b]
Pubmed	((("italy")[Title/Abstract] OR "italian"[Title/Abstract])) AND (("vbhc")[Title/Abstract] OR "value based healthcare"[Title/Abstract])	7	1	1
Scopus	(TITLE-ABS-KEY (VBHC OR "value-based healthcare")) AND (TITLE-ABS-KEY (Italy OR Italian))	2	1	1
Web of Science	TS = ("VBHC" OR "value-based healthcare") AND TS=("Italy" OR "Italian")	1	1	1
Cochane Library	vbhc OR "value-based heathcare") AND (Italy OR Italian) in Title Abstract Keyword	0	0	0
Embase	(vbhc OR 'value-based healthcare') AND ('italy'/exp OR italy OR 'italian'/exp OR italian)	14	1	1
Medline Ovid	(("VBHC" or "value-based healthcare") and (Italy or Italian)).af.	4	0	0
Subtotal		28	4	4
Duplicates				3
Total		28	4	1

[a] Relevant: number of relevant articles based on title, abstract, and keywords

[b] Included: number of included articles based on full article

A2. The Expanded Prostate Cancer Index Composite – Short Form (EPIC-26)

<div style="border: 1px solid black; background-color: #d3d3d3; padding: 20px; text-align: center;">

<u>EPIC-26</u>
The <u>E</u>xpanded <u>P</u>rostate Cancer <u>I</u>ndex <u>C</u>omposite

Short Form

</div>

This questionnaire is designed to measure Quality of Life issues in patients with Prostate cancer. To help us get the most accurate measurement, it is important that you answer all questions honestly and completely.

Remember, as with all medical records, information contained within this survey will remain strictly confidential.

Today's Date (please enter date when survey completed): Month_____Day_____Year_____

Name (optional): _____

Date of Birth (optional): Month_____Day_____Year_____

1. Over the **past 4 weeks**, how often have you leaked urine?

    More than once a day........................ 1

    About once a day............................. 2

    More than once a week.................... 3   (Circle one number)

    About once a week............................4

    Rarely or never................................ 5

2. Which of the following best describes your urinary control **during the last 4 weeks**?

    No urinary control whatsoever........... 1

    Frequent dribbling... 2   (Circle one number)

    Occasional dribbling... 3

    Total control.. 4

3. How many pads or adult diapers <u>per day</u> did you usually use to control leakage **during the last 4 weeks**?

    None 0

    1 pad per day..… 1

    2 pads per day... 2   (Circle one number)

    3 or more pads per day.............................…….. 3

4. How big a problem, if any, has each of the following been for you **during the last 4 weeks**?

    (Circle one number on each line)

		No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
a.	Dripping or leaking urine	0	1	2	3	4
b.	Pain or burning on urination.....	0	1	2	3	4
c.	Bleeding with urination.............	0	1	2	3	4
d.	Weak urine stream or incomplete emptying............	0	1	2	3	4
e.	Need to urinate frequently during the day................................	0	1	2	3	4

5. Overall, how big a problem has your urinary function been for you **during the last 4 weeks**?

    No problem..................................... 1

    Very small problem.......................... 2

    Small problem................................3   (Circle one number)

    Moderate problem........................... 4

    Big problem..................................... 5

6. How big a problem, if any, has each of the following been for you? (Circle one number on each line)

		No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
a.	Urgency to have a bowel movement	0	1	2	3	4
b.	Increased frequency of bowel movements....................	0	1	2	3	4
c.	Losing control of your stools......	0	1	2	3	4
d.	Bloody stools	0	1	2	3	4
e.	Abdominal/ Pelvic/Rectal pain...	0	1	2	3	4

7. Overall, how big a problem have your bowel habits been for you **during the last 4 weeks**?

No problem... 1
Very small problem........................... 2
Small problem................................... 3   (Circle one number)
Moderate problem............................ 4
Big problem....................................... 5

8. How would you rate each of the following **during the last 4 weeks**? (Circle one number on each line)

	Very Poor to None	Poor	Fair	Good	Very Good
a. Your ability to have an erection?................................	1	2	3	4	5
b. Your ability to reach orgasm (climax)?.......................	1	2	3	4	5

9. How would you describe the usual QUALITY of your erections **during the last 4 weeks**?

None at all... 1
Not firm enough for any sexual activity.. 2
Firm enough for masturbation and foreplay only............................. 3   (Circle one number)
Firm enough for intercourse.. 4

10. How would you describe the FREQUENCY of your erections **during the last 4 weeks**?

I NEVER had an erection when I wanted one.................................... 1
I had an erection LESS THAN HALF the time I wanted one............. 2
I had an erection ABOUT HALF the time I wanted one 3   (Circle one number)
I had an erection MORE THAN HALF the time I wanted one............ 4
I had an erection WHENEVER I wanted one..................................... 5

11. Overall, how would you rate your ability to function sexually **during the last 4 weeks**?

Very poor... 1

Poor.. 2

Fair... 3   (Circle one number)

Good.. 4

Very good... 5

12. Overall, how big a problem has your sexual function or lack of sexual function been for you **during the last 4 weeks**?

No problem... 1

Very small problem... 2

Small problem.. 3   (Circle one number)

Moderate problem... 4

Big problem... 5

13. How big a problem **during the last 4 weeks**, if any, has each of the following been for you?
(Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
a. Hot flashes…………...................	0	1	2	3	4
b. Breast tenderness/enlargement..	0	1	2	3	4
c. Feeling depressed….................	0	1	2	3	4
d. Lack of energy…......................	0	1	2	3	4
e. Change in body weight…...........	0	1	2	3	4

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Quality of Life Questionnaire-Core 30 (QLQ-C30)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ☐☐☐☐
Your birthdate (Day, Month, Year): ☐☐☐☐☐☐☐
Today's date (Day, Month, Year): 31 ☐☐☐☐☐☐☐

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a <u>long</u> walk?	1	2	3	4
3.	Do you have any trouble taking a <u>short</u> walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29.   How would you rate your overall health during the past week?

1   2   3   4   5   6   7

Very poor   Excellent

30.   How would you rate your overall quality of life during the past week?

1   2   3   4   5   6   7

Very poor   Excellent

Acknowledgements