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*Review*

# Clustering Diseases in Cancer and Health Organization: What Is the Gold-Standard Approach?

**Tiziana Ciarambino [1,*], Pietro Crispino [2], Ombretta Para [3] and Mauro Giordano [4]**

[1] Internal Emergency Department, Hospital of Marcianise, ASL Caserta, 81037 Caserta, Italy
[2] Emergency Department, Hospital of Latina, ASL Latina, 04100 Latina, Italy; pcrispino@libero.it
[3] Internal Emergency Department, Hospital of Careggi, University of Florence, 50121 Florence, Italy; ombretta.para@gmail.com
[4] Department of Medical Science, University of Campania, L. Vanvitelli, 81100 Naples, Italy; mauro.giordano@unicampania.it
* Correspondence: tiziana.ciarambino@gmail.com

**Abstract:** Cancer is a chronic disease with long-term consequences for health and quality of life and is more prevalent among older people. Therefore, comorbidity among cancer patients is commonly observed. Several data indicate that 40% of cancer patients have at least one other chronic condition recorded, and of these, 15% have two or more medical conditions, including cardiovascular disease, obesity and metabolic disease, mental health problems, and muscle-skeletal conditions. There is no gold-standard approach for measuring comorbidity in the context of cancer, especially in recent years, when health systems have dealt with a pandemic emergency that has negatively impacted the management of cancer patients. The purpose of this narrative review is to clarify and provide the necessary insights to optimize the care of cancer patients. Ensuring the continuum of care for cancer patients is of vital importance and is considered a top priority. It is necessary to overcome the model that considers neoplastic pathology as a single morbid condition. Instead, the complexity of a cancer patient's problems must be considered and related to complex medical conditions. Addressing the problem of comorbidity in cancer more decisively will be a central challenge if we are to avert a crisis in the models of diagnosis and treatment of cancer patients.

**Keywords:** cancer; comorbidity; health organization; gold-standard approach

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## 1. Background

Chronic diseases are generally more common among older adults than younger adults, and though many of these are not life threatening in the short term, they can have serious effects on quality of life. As a result, many people live with chronic diseases that gradually worsen health, rather than dying from a single serious condition [1]. Cancer is a chronic disease with long-term consequences for health and quality of life and is more prevalent among older people. Aging is a determining factor in the development of cancer. In fact, over time, the aging body accumulates the effects of carcinogenic factors, reducing the ability to repair cells. In fact, the incidence of tumors clearly increases with age [2]. Comorbidity among cancer patients is therefore commonly observed. Several data indicate that cancer patients suffer at least one other recorded chronic condition or have two or more medical conditions [1]. The coexistence of cancer and other chronic conditions has major implications for treatment decisions and treatment outcomes for both cancer and its associated chronic diseases [2–7]. Most cancer treatment guidelines, which include conventional therapeutic protocols used in oncology, tend not to consider the complex interrelationships between cancer and comorbidities and instead adopt a single-disease approach, managing almost exclusively the type of oncological condition. Today, with the increase in sub-specialization in medicine and surgery, many healthcare providers are often not sufficiently qualified to manage a wide spectrum of different diseases. This

aspect affects especially cancer patients, and potentially has a negative impact on patient therapies [7].

## 2. Methods

In this narrative review, we included clinical trials published by Pubmed through 28 February 2022. The keywords used were cancer, comorbidity, health organization, and gold-standard approach. All paper and clinical published by Pubmed were studied by two authors. We excluded studies written in languages other than English. Two authors (P.C., T.C.) reviewed all articles and all studies were qualitatively analyzed. The goal of this review is to provide the necessary decision support to public health agencies to promote sound public health approaches, facilitate transparency, and build trust in the community. The review of studies on tumor pathology clusters is difficult to provide definitive answers on the management of the disease. Furthermore, it is inherently difficult to study a cluster for a disease with complex etiology and long latency like most cancers. Despite this difficulty, cluster assessment remains an important function of local, state, and federal public health agencies. Prompt and timely involvement of public health agencies is critical because a poor initial response can result in the loss of opportunities for investigation and education and can increase the level of uncertainty and concern in a community, resulting in the potential need to spend further public health resources later.

*The Concept of Comorbidity and Frailty*

*Comorbidity* is generally defined as the coexistence of one or more disorders alongside a primary disease of interest [8]. In the care of cancer patients, comorbidity represents a substrate of the nature and severity of the health conditions that exist alongside the neoplasm and is distinct from another indicator, which is frailty, and which is more concerned with the preservation of functional status. The prevalence of comorbidities varies based on a patient's non-modifiable factors. Like cancer itself, comorbidity increases in quantity and severity with age, even if the age and quantity of pathological conditions in older people do not necessarily coexist. Comorbidity depends on the patient's social and economic condition, on the possibility of accessing the best center for treatment of every pathology, and on the difficulty of obtaining optimal care at home. Functional status, that is, the measure of a patients' ability to perform daily tasks, is linked to both the presence and consequences of chronic diseases.

*Frailty* is defined as a physiological state of greater vulnerability to stress factors resulting from the variable but predictable decrease from subject to subject in physiological reserves, and from dysregulation of the organism's multiple physiological systems [9]. With respect to comorbidity, frailty is strongly linked to increasing age, and refers to the quality of each subject's senescence [9,10]. Although there is a strong association between them, comorbidities, functional status, and frailty sometimes concur in synergy in determining the clinical result and sometimes have independent effects in determining the predetermined results [3,9].

There is no gold-standard approach to measuring comorbidity in the context of cancer, because so far, no attention has been paid to data retention, resulting in loss of information. Furthermore, where the data have been stored, homogeneous standardized methods have not been used for their management. Both the lack of data collection and the lack of standardized data management methods represent an unsolved problem in defining the correlation between cancer and the coexistence of one or more disorders.

## 3. Results

### *3.1. The Prevalence of Comorbidity in Cancer Patients*

Based on the above and considering that there is general agreement that comorbidity is common among cancer patients, it is difficult to state exactly how the two entities relate to each other. The cause of this is the heterogeneous method of measuring the prevalence of comorbidity in the study population, and the type of cancer. In various studies, comorbidity

had a variable effect on the use of chemotherapy, and different results were observed among patients with solid tumours [11], particularly in older patients. Other studies conducted on cancer patients, based on administrative data, report lower levels of comorbidity than those based on the revision of medical notes or on self-assessment [12–17]. Overall, these results, and those of several other studies [1], are consistent with the presence of a prevalence spectrum of comorbidities among cancer patients. Furthermore, patients diagnosed with cancer are most often those who have pathological conditions most strongly associated with risk factors (especially smoking). There is a wide range of cancer types, such as breast and prostate cancer, which are not strongly linked to environmental factors such as age; these include exposure to ultraviolet (UV) radiation, alcohol use, smoking, and exposure to pollution, all of which further contribute to the chronic accumulation of DNA damage. Data from epidemiological studies suggest that the prevalence of comorbidity tends to be higher among racial/ethnic minority cancer patients and those living with higher levels of deprivation or poverty [18–22]. In some studies, comorbidity has been shown to be partly responsible for disparities in cancer survival among social groups, especially among racial/ethnic groups, compared to general population data [21,23–31].

### *3.2. Mechanisms of Interaction between Neoplasia and Comorbidities*

There is a lot of evidence that comorbidities and their therapies can play a protective or pejorative role, depending on the type of cancer. For example, diabetes has been reported to play a protective role against some forms of cancers of the prostate and lung, and against Hodgkin's lymphoma. On the other hand, patients with diabetes have an increased risk of getting other cancers [32,33]. The different role of metabolic disease is supported by various evidence linking the genesis of tumours with changes in hormone profiles, growth factors, and endogenous steroids [32]. Furthermore, according to various evidence, some treatments for diabetes or obesity, in particular metformin and thiazolidinediones, appear to have antineoplastic activity and may act in reducing the incidence of cancer and slow its progression, probably due to the reduction of cellular proliferation activity [32,34,35].

Similarly, it has been established that the use of non-steroidal anti-inflammatory drugs, commonly used in arthritis and common musculoskeletal diseases, is associated with a reduced risk of colorectal cancer [36,37]. Several studies have hypothesized that there is an inverse relationship between neurodegenerative diseases and cancer [37,38], affirming the presence of a protective balance between the DNA repair mechanisms that promote cell growth and those that inhibit it [38,39]. There may also be interactions between specific tumours with specific comorbid conditions. For example, some studies [40,41] have shown that, among patients on renal dialysis for end-stage renal disease, the possibility of diagnosing cancers of the digestive system occurs earlier, while prostate cancer is usually diagnosed later. This is possible because, in the group of dialysis patients, there is a higher incidence of bleeding or anaemia, and therefore a more frequent use of endoscopic examinations than in the general population. On the contrary, the same authors [40,41] have affirmed that dialysis patients paradoxically underestimate any urinary symptoms, resulting in the subsequent diagnosis of any malignant diseases.

### *3.3. Impact of Comorbidities on the Time to Diagnosis of Neoplasms*

As previously noted regarding the interaction between comorbidities and cancer, the presence of one or more comorbidities plays a double role, positive or negative, on the possibility of tumour diagnosis, and can limit the diagnostic possibilities in various cases of tumours, especially in those where the use of invasive procedures is necessary. In fact, the presence of comorbidities can lead to greater access to health services with consequently greater opportunities for screening and early diagnosis of cancers. The presence of different frailty conditions can cause the professional or the patient to lose interest in tracking health status, which consequently can increase the number of late diagnoses or diagnostic delays. In other cases, the presence of one or more comorbidities prevents the patient from making an exhaustive and complete diagnosis due to the impossibility of performing high-level or

highly invasive diagnostic tests [42–44]. These two mechanisms, as mentioned, do not offer a simple explanation clarifying the relationship between the time of diagnosis of cancer and the type of comorbidity. Numerous studies in different populations indicate that a correct and timely diagnosis of cancer depends on social context, on the local organization of the health system service, and on the geographical distance of the main diagnostic centres that report a broad spectrum of data in comparison to the cancer population without comorbidities [45,46]. According to the literature, the interaction between various factors including those relating to the type of cancer, the type and severity of comorbidities, and the efficiency of the organization of the health system can affect cancer diagnosis [47,48].

### *3.4. Types and Severity of Comorbidities*

According to the literature, patients with one or more comorbidities require more frequent medical visits, and therefore have greater opportunities to undergo screening or to have access to cancer screening investigations early, right from the first symptoms [41–49]. However, an inverse relationship between comorbidities and symptoms has been observed with consequent underestimation of the first manifestations of any neoplastic pathology, since the management of comorbidities can involve the total attention of the staff assigned to such treatments, thus limiting the possibility of an easy diagnosis of cancer. This is likely to be especially true for those with unstable and/or life-threatening conditions [50,51]. Additionally, there may be biological interactions between the specific circumstances of the comorbidity and cancer that may affect the stage of diagnosis. For example, the pathophysiological effects of diabetes mellitus, which results in an increased risk of cancer, may also be associated with more rapidly developing cancers, thereby leading to difficulties in early diagnosis. Siddiqui et al. [52] found that patients with uncontrolled type II diabetes tended to have more advanced forms of colorectal cancer diagnosed at a younger age than those with well-controlled diabetes despite having similar socio-demographic characteristics and equal number of outpatient visits.

### *3.5. The Impact of the Organization of the Health Service*

The organization of health services can have an impact on the way in which comorbidity affects the stage of cancer diagnosis, particularly in the context of mass-screened cancers (Table 1). Cancers that are effectively diagnosed during screening procedures are more susceptible to early detection than other cancers, an effect that is most pronounced in the context of capillary screening [45,53]. Patients with comorbidities access health services more regularly and therefore may be more screened, particularly when screening participation rates are linked to massive funding from the health service or because they constitute quality indicators of the health system [54]. While these studies have shown that screening rates among patients with comorbidities in the context of these methods are like those without comorbidities, other studies [55,56] have not demonstrated this positive synergism, considering the presence of comorbidities an obstacle to achieving a correct diagnosis of cancer. Other authors have stigmatized the excessive use of diagnostic screening tools, often performed improperly in patients with severe comorbidities and limited life expectancy [57–59].

**Table 1.** Type of comorbidities and preventive approaches in the various cancer.

| Tumors | Associate Cluster | Prevention |
| --- | --- | --- |
| Digestive tract cancers | Helicobacter pylori infection. Being overweight or obese. Diet. Alcohol use. Previous stomach surgery, polyps, Pernicious anemia, Menetrier disease (hypertrophic gastropathy), Lynch syndrome (hereditary non-polyposis colorectal cancer, or HNPCC), Familial adenomatous polyposis (FAP), Peutz-Jeghers syndrome (PJS), familiarity. Having type A blood. | Limit alcohol, tobacco products. Avoid eating smoked and pickled foods and salted meats and fish. Diet rich in fresh fruits and vegetables and fiber. Supplementing oral vitamins. Endoscopic screening and surveillance of risk population. H. pylori eradication. Polyps screening and resection. |

**Table 1.** *Cont.*

| Tumors | Associate Cluster | Prevention |
|---|---|---|
| Respiratory tract cancers | Tobacco smoke. Exposure to radon, asbestos, agents in the workplace, Arsenic, radiation therapy, pollution, Chronic Obstructive Pulmonary Disease (COPD) | Avoid smoke. Test home for radon. Avoid carcinogens at work. Eat fruits and vegetables. Exercise most days of the week. Imaging and functional diagnostic strategy screening |
| Femal urogynecological tract cancers | Methylmercury, carbon monoxide, lead, ethylene oxide Cadmium, lead, mercury, chlorinated hydrocarbon solvents. Family history of breast, ovarian, uterine, or colon cancer. Obesity. Diethylstilbestrol (DES) exposure. Human papillomavirus (HPV) infection. | Pap tests, maintaining a healthy diet and lifestyle, genetic testing, and the HPV vaccine are at the forefront of gynecologic cancer prevention. Diet rich in fruit and vegetables |
| Male urogynecological tract cancers | Methylmercury, carbon monoxide, lead, ethylene oxide Cadmium, lead, mercury, chlorinated hydrocarbon solvents. Infection. Tobacco consuming. Family history. Eating habits. Agent Orange exposure. | Chemoprevention especially in prostate cancer. Dietary changes. PSA blood test. Ultrasound screening test. Urinary test. Limiting exposure to toxic agents, especially in the workplace. |
| Breast cancer | Genetic mutations. Having dense breasts. Personal history of breast cancer or certain non-cancerous breast diseases. Family history of breast or ovarian cancer. Previous treatment using radiation therapy. Exposure to the drug diethylstilbestrol (DES). Hormonal therapies. Drinking alcohol, obesity, Not breastfeeding, Menopausal hormone therapy. | Limit alcohol. Maintain a healthy weight. Be physically active. Breast-feed. Limit postmenopausal hormone therapy. Lifestyle and diet modification, vitamins, and micronutrient supplementation. Routine breast screening |
| Nervous system cancers | Home and work exposures to electromagnetic fields and ionizing radiation. Family history. Exposure to infections, viruses, and allergens. Hereditary genetic factors or conditions, including Li-Fraumeni syndrome, neurofibromatosis, nevoid basal cell carcinoma syndrome, tuberous sclerosis, Turcot syndrome, and von Hippel-Lindau disease. | Reduce the risk of developing a brain tumor by avoiding environmental hazards such as smoking and excessive radiation exposure. |
| Skin cancers | Exposure to the sun with ultraviolet rays. Dioxin, nickel, arsenic, mercury, cement (chromium), polychlorinated Biphenyls (PCBs), glues, and rubber cement. A family history of skin cancer. A personal history of skin cancer. Older age. | Seek the shade, especially between 10 AM and 4 PM. Don't get sunburned. Avoid tanning, and never use UV tanning beds. Use a broad-spectrum (UVA/UVB) sunscreen. Adhering strategy prevention of melanoma using epiluminescence |
| Hepato-biliary tract cancers | Carbon tetrachloride, methylene chloride, vinyl chloride. Smoke, Obesity (body mass index >30 kg/m$^2$). Heavy alcohol use, Long-standing diabetes (>5 years). Hepatitis B and C Infection, Nonalcoholic fatty liver disease (NAFLD), Hemochromatosis, male hormones or anabolic steroids, Ingestion of aflatoxin. | Maintaining a healthy weight, stopping smoking, and limiting your alcohol intake. Avoid and treat hepatitis B and C infections. Limit exposure to cancer-causing chemical agents. Treat diseases that increase liver cancer risk. |
| Hematological cancers | Arsenic, nitrates, radiation Smoking, radiation exposure, and exposure to chemicals such as benzene (a widely used industrial chemical) have all been linked to an increased risk of some types of blood cancers. Epstein-Barr virus, HIV, and human T-cell lymphoma/leukemia virus infections. Chemotherapy Drugs | Avoid exposure to radiation, chemicals such as pesticides or benzene, and smoking or tobacco in any form. Additional lifestyle behaviors, such as staying active and eating a healthy diet can help reduce your risk of developing a variety of cancers and other diseases. Periodical hematochemical controls |

### *3.6. Impact of Comorbidity on the Choice of Treatment for Neoplasms*

Comorbidity patients are less likely to receive curative treatment for cancer than those with non-comorbid cancer [11,60–70]. Taking colorectal cancer as an example, numerous studies have found that the possibility of fully implementing chemotherapy protocols in these patients is lower among patients with comorbidities regardless of age [71–74]. The relationship between the number and type of co-morbidities and surgical treatment is less clear, with some studies reporting no association, and others showing an inverse relationship between increased comorbidity and decreased probability of surgery or reduced quality of surgical care for those with comorbidity [73,75–77]. Although most studies report that cancer patients with comorbidities receive less treatment than cancer patients

without associated conditions, some studies have sometimes reported the presence of overtreatment in cancer patients with comorbidities [78]. Clinical evidence-based studies demonstrate the need to base decisions in cancer patients based on the number and type of comorbidities [79–81]. In the context of multi-disciplinary teams, in which many cancer treatment decisions are made, there is resistance to initiating chemotherapy in comorbid cancer patients [82]. There are numerous factors that can explain the negative effect of comorbidities with respect to a successful treatment outcome, starting with an increase in toxicity and side effects related to chemotherapy. It also seems clear that according to most clinicians in comorbidity patient groups, the treatments are less effective in these groups, and that the reduced life expectancy of these patients is a sufficient factor to sometimes justify the withdrawal of potentially harmful toxic agents [72,73,83–85]. It is also possible that these patients themselves refuse treatment, while it seems clear that cancer patients with comorbidities are usually less likely to receive curative treatment [84–86]. This is explained by the lack of significant evidence from the randomized controlled trials (RCTs) that often exclude older patients or those with comorbidities, which suggests that most therapeutic schemes are not directly applicable to these cancer patients [87,88].

### *3.7. Impact of Comorbidities on the Outcome of Cancer Treatment*

The extent to which comorbidity can affect the success of treatments depends on the type and severity of the conditions and on the specific treatment to be implemented. For example, patients with severe chronic respiratory disease would hardly tolerate a pneumonectomy for lung cancer but could tolerate treatment that does not affect their already precarious respiratory function. Patients with severe renal damage would hardly tolerate a chemotherapy scheme conducted with nephrotoxic drugs but could benefit from other chemotherapy drugs. Numerous authors [89–96] have reported that, in general, comorbidity does not increase the frequency or severity of treatment-related complications. In contrast, other studies have reported higher complication rates among cancer patients with comorbidities [11,18,64,97–100] including patients treated only with surgery for curative removal of a neoplasm [97–100]. Studies evaluating the impact of comorbidity on the treatment of cancer have shown better survival in well attended patients with clinical conditions in equilibrium, compared to those who are not [72,78,101–103]. The interpretation of all these results, however, is always complicated by the fact that most clinical studies on cancer exclude patients with significant comorbidity, which makes it difficult to evaluate the real efficacy and toxicity of the treatment by comparing the results obtained in patients of cancer with and without comorbidities [88]. It was observed that patients with important comorbidities have the possibility of being treated and therefore of having better results than patients considered to be healthier [78,88,102,103]. The use of propensity scores could prove beneficial because they provide the possibility of determining the probability of success that an individual undergoing treatment has, regardless of whether he has received treatment [104]. Patients with similar propensity scores can be treated for malignancy and then their therapeutic results can be compared, depending on whether they received treatment. Bradley and colleagues [78] studied elderly prostate cancer patients with and without comorbidities, dividing their sample into men with high-risk, intermediate-risk, and low-risk prostate cancer, then calculated their propensity scores to determine the likelihood of receiving treatment. They found that men with both intermediate-risk and high-risk prostate cancer who were treated had substantially better survival rates than those who were not treated, with no difference in comorbid status [78]. Similarly, an observation of elderly patients with colorectal cancer showed that, by applying the propensity scores, there was less possibility of treatment in patients with comorbidities and advantage in survival in those with comorbidities who had been treated with curative intentions compared to those who had not [88]. These findings suggest that some comorbidity patients may benefit from potentially curative treatment. Another important consideration is the impact of cancer treatment with the interaction of other drugs. Patients with comorbidities certainly have a greater pharmacological load, which can interact with chemotherapeutic

agents, potentially leading to greater toxicity and a reduction in the efficacy of a therapeutic regimen [104–107]. The few studies that have been done suggest that about one-third of treated cancer patients are exposed to potential interactions [108,109] and about one in ten unplanned hospitalizations of cancer patients are related to adverse drug reactions. It has been reported that polytherapy is associated with an increased risk of toxicity of chemotherapeutic agents compared to therapy with one or a few drugs [110,111]. In summary, while there is evidence that some cancer patients with comorbidities may be at an increased risk of post-therapeutic complications, this is not a constant occurrence. The extent to which treatments are tolerated will, of course, depend on several interacting and complex factors, including cancer treatment and the number, type, and severity of the specific comorbidities involved. However, what is clear is that there is substantial inconsistency in treatment decisions based on comorbidities and the lack of consensus on what should be done. It is possible that the lack of demonstrable differences in tolerability and treatment efficacy in patients with and without comorbidities suggests that the treatment recommendations available in the literature regarding these groups may not always be justifiable considering their actual clinical conditions.

### *3.8. Impact on Survival*

Comorbidity has always been considered to have a negative impact on cancer survival [3,6,11] (Figure 1). The impact of comorbidity tends to increase with the increasing severity of clinical conditions, although not necessarily linearly [78,84,112]. Very high levels of comorbidities are often associated with a considerably higher risk of death than no comorbidities. The impact of comorbidity on cancer-specific survival is less constant and variable, depending on cancer prognosis, stage, treatment effect, and severity of comorbidity [1,6]. The impact of comorbidity tends to be greater for tutors with a better prognosis [113–116] while those affected by cancer associated with a high mortality rate will be more likely to die from same cancer, regardless of other concomitant diseases than patients who have a less severe prognosis. For example, Piccirillo et al. [114] have covered that, the impact of comorbidity is greater for cancer diagnosed at an early stage than for advanced cancer. There are several reasons why comorbidity impacts survival. The most obvious is the direct and independent impact of the concomitant disease on non-cancer mortality. In addition, cancer-specific survival can sometimes be reduced among those with comorbidities. A possible explanation for this is related to the fact that some cancer patients who die from circumstances related to comorbidities are wrongly categorized as dying of their cancer [117]. As described above, there is evidence that cancer patients with comorbidities receive less effective treatment than those without, and this has a major impact on their likelihood of survival. Comorbidity patients may also experience higher levels of treatment toxicity, negatively impacting their cancer-specific survival [11]. Another mechanism of interaction between comorbidity and survival is through a direct effect of the former on cancer progression. Meyerhardt et al. [89] studied the prognosis of patients with and without diabetes on adjuvant therapy for colon cancer, finding that diabetics had an increased risk of relapse. Piccirillo et al. [115] found that the likelihood of developing cancer recurrence increases proportionally with an increasing level of comorbidity. In contrast, Kiderlan [118] observed that, among breast cancer patients, those with diabetes have a lower relapse rate linked to the favorable effect of metformin in counteracting neoplastic growth.

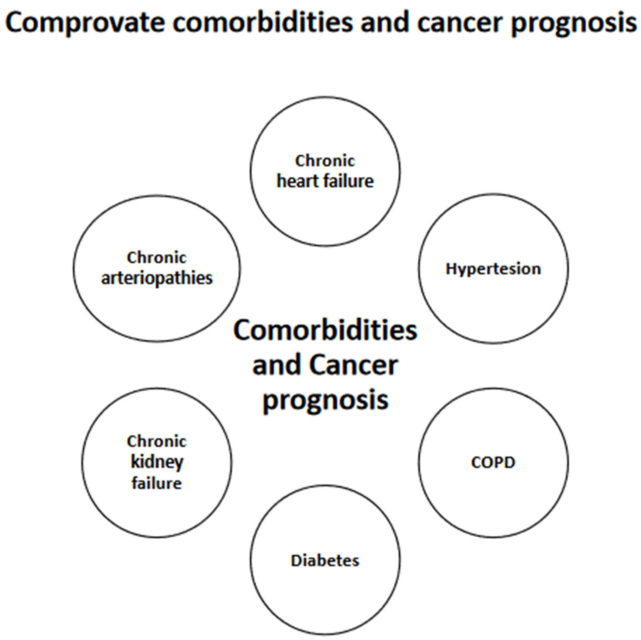


**Figure 1.** Comprovate comorbidities and cancer prognosis.

*3.9. Impact on Quality of Life*

Non-cancer studies have always associated comorbidity with a poorer quality of life [119–122]. There are few studies that investigate the subject in cancer patients. In a group of lung cancer patients, Gronberg et al. [91] found that all patients had poor quality of life and that this did not depend on the comorbid state. Studies on patients with early-stage prostate cancer have suggested that comorbidity leads to a lower quality of life during the treatment period but is common to all patients with the same cancer without other pathologies [123,124]. However, higher levels of disease, related to a delay in cancer diagnosis, are correlated with greater health care needs, greater likelihood of disability, higher costs of care, and higher financial commitment, and therefore to greater socioeconomic disadvantage [125–127] (Figure 2).

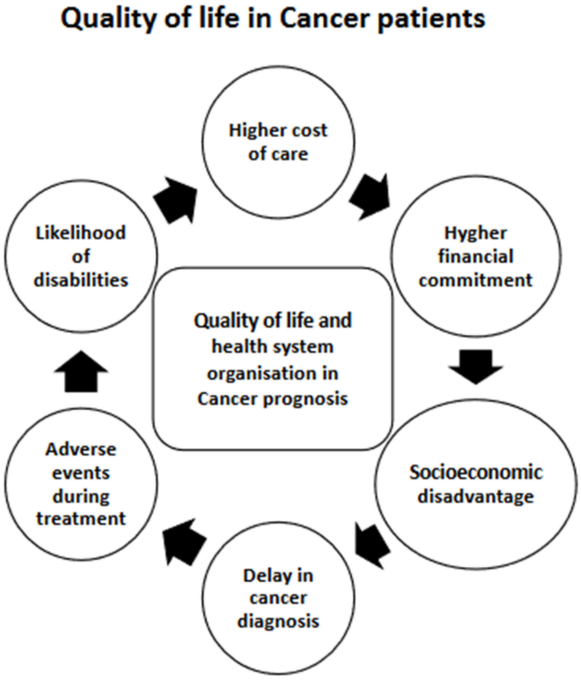


**Figure 2.** Quality of life in cancer patients.

### 3.10. Impact of Cancer Treatments on Comorbidities

In addition to the impact of comorbidities on the outcome of cancer treatments, it is worth noting that cancer itself, or more specifically, the treatment, can influence the results related to the treatment of comorbidities. Cancer therapies can increase the risk of cardiovascular, metabolic, musculoskeletal, and other diseases, and can worsen pre-existing comorbidities. For example, metabolic changes associated with hormone treatment for cancer can lead to worsening diabetic control and an increased risk of diabetes-related complications [128]. Many chemotherapeutic agents are implicated in the development of heart failure [129]. Androgen deprivation therapy for prostate cancer is associated with an increased risk of cardiovascular problems and worsening of pre-existing heart disease [130,131]. Furthermore, hormone treatment for breast and prostate cancer is known to lead to or aggravate osteoporosis [132,133]. In addition to these direct effects, it is likely that, during cancer treatment, there may be a lack of attention to chronic disease management by both patients and clinicians, which, in turn, can negatively impact overall care outcomes. Little is known about how much cancer and its treatment impact the treatment outcomes of comorbidities, in part because patients with significant comorbidities are usually excluded from clinical trials, and in part because most of the data for cancer patients are concentrated on the evaluation of cancer-specific outcomes rather than on the evaluation of outcomes related to other conditions.

### 3.11. COVID-19 and Management of Cancer Patients

Cancer is a disease characterized by uncontrolled cell growth that can involve any tissue in the body and has the potential risk of spreading to target organs by contiguity or direct invasion, by haematogenic, lymphatic, and more rarely, neurogenic routes. The most frequently used cancer treatments work by killing or blocking the growth and spread of rapidly dividing cancer cells in target organs. However, some cancer treatments suppress other rapidly growing cells, such as white blood cells, and the cancer itself can affect the immune system by spreading to the bone marrow. Therefore, people with weak immune systems have a higher risk of getting frequent infections and are more likely to get COVID-19. The increased susceptibility of cancer patients to the serious complications of COVID-19 can be attributed to the state of immunosuppression caused by anticancer treatments, such as chemotherapy or surgery. Immunosuppression can also expose cancer patients to serious complications from an infection, which can lead to delayed treatment and unnecessary hospitalizations that could adversely affect disease prognosis. It has also been shown that patients undergoing different types of cancer treatment show disparity in response to COVID-19 compared to non-cancer patients. Finally, patients who received immunotherapy or surgery tend to have higher death rates and a greater chance of developing critical symptoms than those who received chemotherapy or radiotherapy [134–136]. Liang et al. [137] showed that patients who had undergone cancer-type surgery in the 30 days prior to presenting with COVID-19 had a greater risk of serious events than patients who had not been treated with chemotherapy or surgery. Cancer history was also found to confer the highest risk of serious complications and correlated with worse outcomes from COVID-19. Liang et al. [137] demonstrated that patients with cancer consistently show a higher risk of serious infections, with an approximately 3.5-fold increased risk of needing mechanical ventilation, intensive care unit (ICU) admission, or death compared to patients without cancer. Today, there are no sufficiently shared guidelines regarding the association of COVID-19 infection and the management of cancer patients. The same authors [137] indicated three strategies that may be applied to cancer patients during the COVID-19 pandemic: postponing chemotherapy treatment or elective surgical procedures in stable cancer cases, implementing strict personal precautions in cancer patients or cancer survivors, and providing more intensive care and treatment to cancer patients with COVID-19. These strategies may not be wholly sufficient since they do not consider elderly patients or those who may have other comorbidities. In our opinion, the cancer patient's demand for care must be managed by creating paths within the cancer centres, capable of combining

treatment efficacy and safety [137]. This would have been possible by placing hospitals and cancer centres in a common network, giving space to multidisciplinary teams, and more effectively separating these patients from the flow of those who crowded emergency and intensive care facilities during the pandemic. Ultimately, the demand for treatment of cancer patients had to be conveyed to suitable structures where every moment of treatment was guaranteed in complete safety and was effective in contrasting the progression of cancer.

#### 3.11.1. A. Risk Factors Associated with the Severity of COVID-19 in Cancer Patients

From the data available in the literature [138–140], severe COVID-19 disease and mortality in cancer patients are significantly associated with advanced age and disease severity, especially the pulmonary pathological picture, the presence of multiple comorbidities, and harmful habits such as cigarette smoking. Mehta et al. [138] demonstrated that advanced age in cancer patients is significantly associated with increased mortality, more severe disease manifestation, and an increased need for ventilatory support or intensive care. It is interesting to note that, in this study, there was no statistically significant difference between advanced metastatic tumour disease or localized tumour and death from COVID-19 [138]. Furthermore, patients undergoing chemotherapy or radiotherapy did not show a significant difference in COVID-related deaths compared to patients currently not on treatment. Conversely, comorbidities, including heart disease (hypertension, coronary heart disease, congestive heart failure) and chronic lung disease led to an increased risk of COVID-19-related deaths in cancer patients [138]. Furthermore, the same study and other studies [139,140] admitted that cancer patients die predominantly in old age, but the mortality rate is significantly higher in all age groups than in for non-cancer patients, suggesting the COVID-19 virus affects cancer patients more severely than the general population. Additionally notable are the data regarding the severity of COVID-19 in lung cancer patients, where a worse prognosis was observed in those with advanced age, history of smoking, chronic obstructive pulmonary disease (COPD), and chronic heart failure [141] (Figure 3). However, the severe disease and mortality rate from COVID-19 did not differ in patients receiving chemotherapy or tyrosine kinase inhibitors compared to other patients with lung cancer [141]. Another study conducted by Garassino et al. [142] considered patients with thoracic malignancies, showing that age (>65 years), cigarette smoking, chemotherapy treatment, and any comorbidities were associated with an increased risk of death due to COVID-19.

The evidence that emerged from patients with haematological malignancies and concomitant COVID-19 infection is also of great interest. Passamonti et al. [143] found in an observation study that the main risk factors associated with worse overall survival were advanced age, the level of disease progression, the diagnosis of acute myeloid leukaemia, indolent non-Hodgkin's lymphoma, aggressive non-Hodgkin's lymphoma or plasma cell neoplasms, and severe pulmonary involvement of COVID-19 infection. Furthermore, patients were at higher risk of mortality regardless of whether they had recent illness or were on specific therapy, or both [144]. Active chemotherapy treatment and viral load at diagnosis were not predictors of COVID-19 hematologic patient mortality [139,145]. As we have seen, multiple prognostic variables have been associated with COVID-19-related mortality in cancer patients, such advanced age, male sex, cigarette smoking, number of comorbidities, and the presence of solid versus haematological tumours. Instead, race, ethnicity, obesity, malignancy, or type of cancer treatment were not associated with high mortality [136,145].

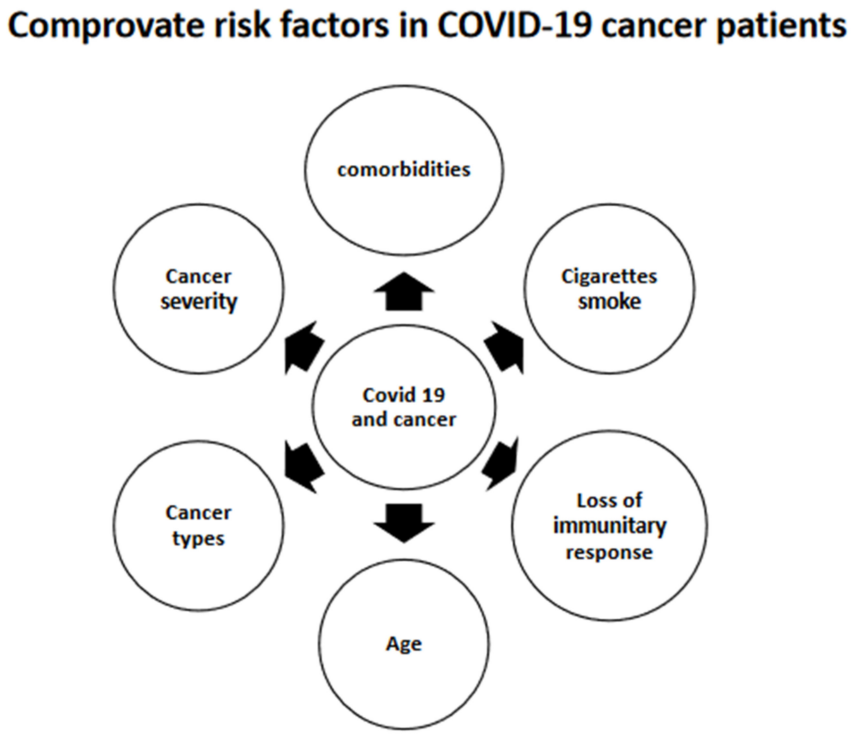


**Figure 3.** Comprovate risk factors in COVID-19 cancer patients.

3.11.2. B. Health Organization and Cancer Treatment in the Pandemic Period

Wang and Zhang [146] pointed out that, during the COVID-19 pandemic, the main risk for cancer patients was limited access to necessary health care and the inability to receive necessary medical services in a timely manner, especially in high-risk epidemic areas where a large percentage of medical personnel and health facilities were required for the fight against the pandemic. In our opinion, the limited access to treatment of cancer patients was not only a problem in the areas with the highest incidence but also in other areas, not necessarily those with a high population density, but also in more isolated areas, in which the most advanced treatments in the oncology field were unavailable. The blocking of diagnostics, outpatient services, surgical interventions in the oncological field, and the administration of chemotherapy and radiotherapy sessions led to a worsening of mortality and disease progression in patients under treatment. During the most critical period of the pandemic, the rationing of care, the cancellation of appointments, and the postponement of surgeries led to difficult decisions. In the case of critically ill patients, care plans had to be revised and end-of-life plans and palliative care had to be revisited. Faced with limited resources during the COVID-19 pandemic, greater organizational effort was required, making the formation of multidisciplinary cancer treatment teams including medical ethics experts and palliative care specialists far more difficult. In this scenario, it was very difficult and complicated to decide which patients should undergo more intensive therapies because they were complicated or critical, and it was difficult to postpone the appropriate treatments, having to review the outcomes for each patient, without being able to obtain the expected clinical results [147]. The experience of the pandemic in the future will have to involve greater levels of organization of our health systems to guarantee the most appropriate treatments for all while still adhering to high safety standards.

## 4. Future Directions

The multitude of challenges related to the coexistence of comorbidities and cancer require a multidisciplinary approach to address them with solutions ranging from clinical practice to research. Below is a list of key strategies that offer hope for progress in this area (Figure 4).

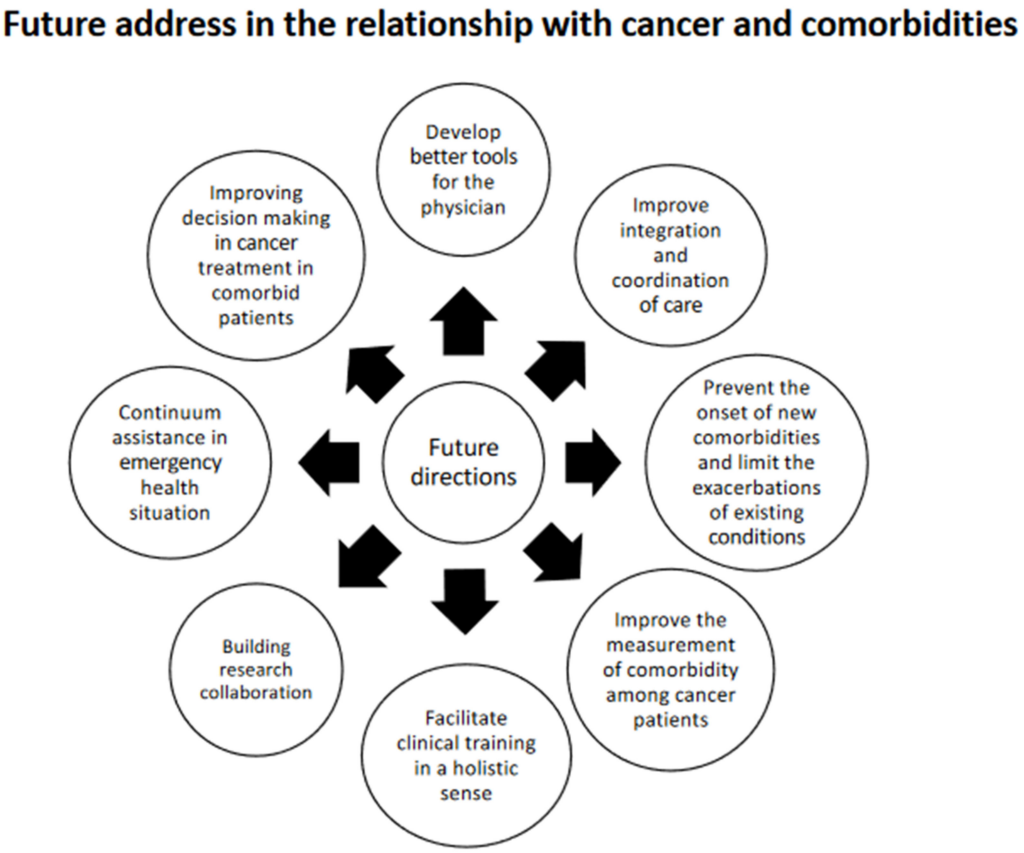


**Figure 4.** Future address in the relationship with cancer and comorbidities.

## 5. Preventive Measures for Clustering Disease

- Improving decision making in cancer treatment in comorbid patients

We have seen how RCTs frequently exclude older patients or those with comorbidities. It is recommended that researchers evaluate interventions and technologies in at-risk populations by more closely analyzing the age distribution and health risk profile of cancer patients. Interventions by pharmaceutical companies are suggested to promote clinical trials of cancer treatments in elderly patients or patients with comorbidities [7]. Similarly, research-funding bodies may require cancer treatment studies to be carried out within these populations.

- Improve the measurement of comorbidity among cancer patients

To better understand the influence of comorbidity on efficacy in cancer treatment, the former must be measured with greater precision. First, it is necessary to recognize comorbidity as an important variable to be considered as a determinant of the success of cancer diagnosis and therapy. Second, careful consideration is required regarding how best to measure the impact of comorbidities on the overall care outcomes of cancer patients. Some guidelines are already present in the literature and should help to take measures in this direction [148,149]. The impact of comorbidities in cancer care and outcomes should be examined both from the perspective of people with cancer (such as the impact of comorbidities on survival, disability, and individual costs of care), and from the perspective of the health system (such as the overall cost of care and use of health care).

- Improve integration and coordination of care

Mismanagement of patients with multiple health problems can lead to fragmentation in care. The coordination of care has previously been identified as critical for both the effective delivery of cancer care and effective care for those with multiple chronic

conditions [150,151]. It is essential to ensure that coordination and integration of care extends beyond the domain of cancer and includes all other patient needs. There are many approaches that can be helpful in improving the coordination of care for cancer patients within and outside cancer care services, including growing collaboration with primary care services, more effectively using technology, distributing health information to facilitate coordination, and sharing and promoting intervention plans [7,150,151]. It is likely that the usefulness of each model will depend on the context and setting, and in the future, more effort will be required to evaluate which models are the most useful and convenient in setting up cancer treatment. The use of comprehensive geriatric assessments in geriatric oncology provides an excellent example of integrated care. Complete geriatric assessments provide data on the patient's functional status, comorbidity, polytherapy, the existence of geriatric syndromes, nutritional status, social support, and psychological status. Many studies show that incorporating such assessment into the care of older people with cancer can be useful in predicting complications of care, estimating mortality or survival, and assisting in the decision-making process [152–161]. More effort is needed to assess whether such wide-ranging interventions are generally beneficial (even for non-geriatric patients with comorbidities) and whether they are profitable in terms of resource optimization [162].

- Prevent the onset of new comorbidities and limit the exacerbations of existing conditions

New comorbidities can emerge during or after cancer and cancer treatment, and the latter can exacerbate the underlying circumstances. So far, most research has focused on managing comorbid conditions among cancer survivors, whereas there is very little research on the impact of careful comorbid management and polypharmacy in the patient's active treatment phase oncology [161,162]. Furthermore, research has shown that polypharmacy and adverse drug reactions are important causes of unplanned hospitalization and higher toxicity rates [108–111]. Yet the studies that have been conducted to date are small and insufficient in terms of knowledge of the frequency, severity, and effect of drug interactions during cancer treatment. Furthermore, it would be useful to understand whether an intervention to reduce polypharmacy among cancer patients receiving chemotherapy can improve the survival of such patients [163–167].

- Develop better tools for clinicians

There have always been limited resources available to clinicians for managing multiple health care problems affecting patients with comorbidities or for providing accurate prognostic information regarding cancer interaction outcomes and coexisting conditions. Some decision aids have been developed in the context of geriatric oncology, including the impact of all chronic diseases on survival or life expectancy, which have proven useful in evaluating treatment decisions for people with comorbidities [168,169].

- Facilitate clinical training in a holistic sense

Today, most physician training programs focus on the development of specialists rather than focusing on knowledge and skills in a holistic sense. Specialist knowledge is clearly required in cancer management. However, current models of cancer care require new skills for health care providers, and still further efforts are needed to develop skills and capabilities among both cancer care professionals as well as those who are not directly involved in cancer care. Skills include understanding the risk, prevalence, and management of comorbidities in cancer, a but also the ability to achieve integration of care and communication between the various professionals who deal with the health of the cancer patient [170].

- Building research collaborations

Many of the proposed strategies are currently in an early stage of development and are not yet ready to be adapted to routine clinical practice. Research is needed in the field of epidemiology regarding cancer comorbidities, their mechanisms and models of care, and the execution of the latter. To truly accelerate research work in this area, it is essential that strong research collaborations be built in both medicine and the cross-disciplinary

multidisciplinary field to be implemented with disciplines including epidemiology, biology, cancer medicine, population health and human research.

- Continuum of assistance in emergency health situations

Ensuring the continuum of care for cancer patients is of vital importance and is considered a top priority in this pandemic period, as many hospitals and health centres have been overwhelmed by the increase in the number of COVID-19 cases, and from the high application for unforeseen medical services for a particularly large number of cases. During the COVID-19 virus epidemic, greater use of online medical advice and telemedicine were necessary, moving treatments to the homes of cancer patients. It would have been beneficial to identify, in the oncology centres of territorial reference, the places to be reserved for the most appropriate diagnoses and treatments of critical cancer cases to minimize the exposure of patients to COVID-19. Using outpatient health facilities for the medical treatment of cancer patients and more effective screening to exclude COVID-19 infection before hospitalizing patients would have preserved the hospitals involved in the emergency by allocating local cancer centres to oncological care. Comprehensive multidisciplinary assistance, including the presence of experts in palliative and end-of-life care, would be desirable in the management of the critically ill patient in health emergencies, such as that of COVID-19. Clinical judgment is of fundamental importance in determining crucial choices, and from an ethical point of view, regarding the continuation or suspension of cancer therapy in patients with COVID-19. It would also be necessary that healthcare professionals who take care of cancer patients have greater access to professional updating of literature data, given the rapid evolution of the flow of information relating to the delicate relationship between cancer and COVID-19 to provide management based on scientific evidence on a case-by-case basis, and to address any new pandemic challenges in the future.

## 6. Conclusions

With a population increasingly predisposed to aging and a growing number of patients diagnosed with cancer, the management of comorbidities assumes an increasing role in modern health services. To address this growing challenge, we need to go beyond the current model that considers cancer as a single morbid condition; we need to consider cancer as part of the complexity of people's problems and relate it to complex medical conditions. Measures should be taken to improve the measurement of comorbidities among cancer patients, decision-making regarding cancer patients, integration and coordination of care, prevention of the onset of new comorbidities by limiting exacerbations of existing conditions and ensuring the continuum of assistance in health emergency situations, focusing on holistic medicine and better collaboration between professionals of the various health systems. These considerations may constitute the foundations of a new way of meeting the needs of cancer patients.

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