Urologia Internationalis

Review

Gian Maria Busetto [a]   Angelo Porreca [b]
Francesco Del Giudice [a]
Martina Maggi [a]   Daniele D'Agostino [b]
Daniele Romagnoli [b]   Gennaro Musi [c]
Giuseppe Lucarelli [d]
Katie Palmer [e]
Ascanio Colonna di Paliano [f]
Matteo Muto [g]   Rodolfo Hurle [h]
Daniela Terracciano [i]
Ottavio de Cobelli [c]
Alessandro Sciarra [a]
Ettore De Berardinis [a]   Matteo Ferro [c]

SARS-CoV-2 Infection and High-Risk Non-Muscle-Invasive Bladder Cancer: Are There Any Common Features?

[a] Department of Urology, Policlinico Umberto I, Sapienza University of Rome, Rome, Italy;
[b] Department of Urology, Abano Terme Policlinic, Abano Terme, Italy; [c] Division of Urology, IEO European Institute of Oncology IRCCS, Milan, Italy; [d] Urology, Andrology and Kidney Transplantation Unit, Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy; [e] Department of Internal Medicine and Geriatrics, Cattolica del Sacro Cuore University, Rome, Italy; [f] Digital Design Kingdom, Rome, Italy; [g] Radiotherapy Unit, S.G. Moscati Hospital, Avellino, Italy; [h] Department of Urology, Humanitas Research Hospital, Milan, Italy; [i] Department of Translational Medical Sciences, University of Naples Federico II, Naples, Italy

Abstract

Background: The new severe acute respiratory syndrome virus (SARS-CoV-2) outbreak is a huge health, social and economic issue and has been declared a pandemic by the World Health Organization. Bladder cancer, on the contrary, is a well-known disease burdened by a high rate of affected patients and risk of recurrence, progression and death. **Summary:** The coronavirus disease (COVID-19 or 2019-nCoV) often involves mild clinical symptoms but in some cases, it can lead to pneumonia with acute respiratory distress syndrome and multiorgan dysfunction. Factors associated with developing a more severe disease are increased age, obesity, smoking and chronic underlying comorbidities (including diabetes mellitus). High-risk non-muscle-invasive bladder cancer (NMIBC) progression and worse prognosis are also characterized by a higher incidence in patients with risk factors similar to COVID-19. Immune system response and inflammation have been found as a common hallmark of both diseases. Most severe cases of COVID-19 and high-risk NMIBC patients at higher recurrence and progression risk are characterized by innate and adaptive immune activation followed by inflammation and cytokine/chemokine storm (interleukin [IL]-2, IL-6, IL-8). Alterations in neutrophils, lymphocytes and platelets accompany the systemic inflammatory response to cancer and infections. Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio for example have been recognized as factors related to poor progno-

Gian Maria Busetto
Policlinico Umberto I, Sapienza University of Rome
Piazzale Aldo Moro, 5
IT–00185 Rome (Italy)
gianmaria.busetto @ uniroma1.it

sis for many solid tumors, including bladder cancer, and their role has been found important even for the prognosis of SARS-CoV-2 infection. ***Key Messages:*** All these mechanisms should be further analyzed in order to find new therapeutic agents and new strategies to block infection and cancer progression. Further than commonly used therapies, controlling cytokine production and inflammatory response is a promising field.

<div align="right">© 2020 S. Karger AG, Basel</div>

Introduction

The new severe acute respiratory syndrome SARS-CoV-2 outbreak in Italy, and in the rest of Europe, is a huge health, social and economic issue that is changing lives worldwide and was declared a pandemic by the World Health Organization. To date (May 15, 2020), more than 200,000 cases of coronavirus disease (COVID-19 or 2019-nCoV) have been registered in Italy with numbers increasing daily (Fig. 1). In this century global health has been already threatened by two severe coronavirus acute respiratory infections: SARS-CoV in 2002 and MERS-CoV in 2012. Coronaviruses are single-strand positive RNA viruses that mainly attack the respiratory system. In the case of COVID-19, clinical symptoms are usually mild but in some cases it can lead to pneumonia with acute respiratory distress syndrome (ARDS) and multiorgan dysfunction requiring hospitalization and intensive care unit (ICU) support [1]. In approximately 7% of cases it leads to death, although the case-fatality rate will not be accurately established until after the outbreak [1]. Virus proteins support a strong interaction with human angiotensin-converting enzyme 2 (ACE2) with activation of the immune system and inflammatory response followed in severe cases by degeneration (necrosis), infiltration and hyperplasia of pulmonary tissue, particularly in the interstitial arteriolar walls leading to reduced lung capacity and functional impairment [2]. Interestingly COVID-19 patients who develop ARDS, suffering from worse prognosis and more severe disease, are very often older persons and those affected by one or more underlying chronic conditions like diabetes mellitus (DM), hypertension and cardiovascular disease [3]. When compared with COVID-19 patients without ARDS, patients with ARDS are generally older and have a higher proportion of comorbidities, and there are more observations of neutrophilia associated with lymphocytopenia, neutrophil-to-lymphocyte ratio (NLR) increase, increase in several inflammation indices (including interleukins, IL-2

and IL-6, tumor necrosis factor α, C-reactive protein and many other cytokines), elevated coagulation function and alteration of other organ dysfunction indices (liver, kidney, etc.) [4].

On the other side, bladder cancer is the 7th most frequent cancer in men and 17th in women. The majority of patients develop a non-muscle-invasive bladder cancer (NMIBC), which involves a heterogeneous tumor associated with high recurrence (up to 70%) and progression rates (up to 30%) [5]. The clinical prognosis of high-risk NMIBC is often difficult to predict, and even when it is treated with transurethral resection of the tumor (TURB) followed by maintenance bacillus Calmette-Guérin (BCG) it can have a heterogeneous prognosis [6]. The best surveillance strategy should be performed with an accurate risk stratification and identification as indolent from aggressive NMIBC. In the era of precision medicine, a model based on standard clinicopathological features (T stage, grade, focality, tumor size, lymphovascular invasion, concomitant carcinoma in situ) should be overcome in favor of more reliable biomarkers able to better understand tumor behavior and to personalize treatment [7].

In particular, the role of inflammation and the immune system are among the main research fields for better understanding the association with tumor recurrences and progression to metastasis [8]. Among inflammation markers, the NLR has been described as promising for bladder cancer, and its increase has been associated with worse cancer specific survival and overall survival [7–9]. A recent systematic meta-analysis described the clinical relevance of NLR for better understanding the prognosis of bladder cancer [10].

Another interesting research area is the possible association of comorbidities with cancer evolution. In particular, there is a focus on understanding metabolic mechanisms that have been described for certain diseases. One of the most studied is DM, and there are some reports that define it as a negative prognostic factor [11], a possibility due to a correlation with inflammation and immune system altered function [11]. Finally aging may increase or decrease the susceptibility of various tissues to carcinogenesis. In fact, unrestrained expression and production of inflammatory mediators is a feature at the cellular and organism level, and structural alteration of the immune system accompanies this process [12].

The aim of the current paper is to analyze two completely different diseases with their known biological and pathological characteristics to examine whether common features can be found.
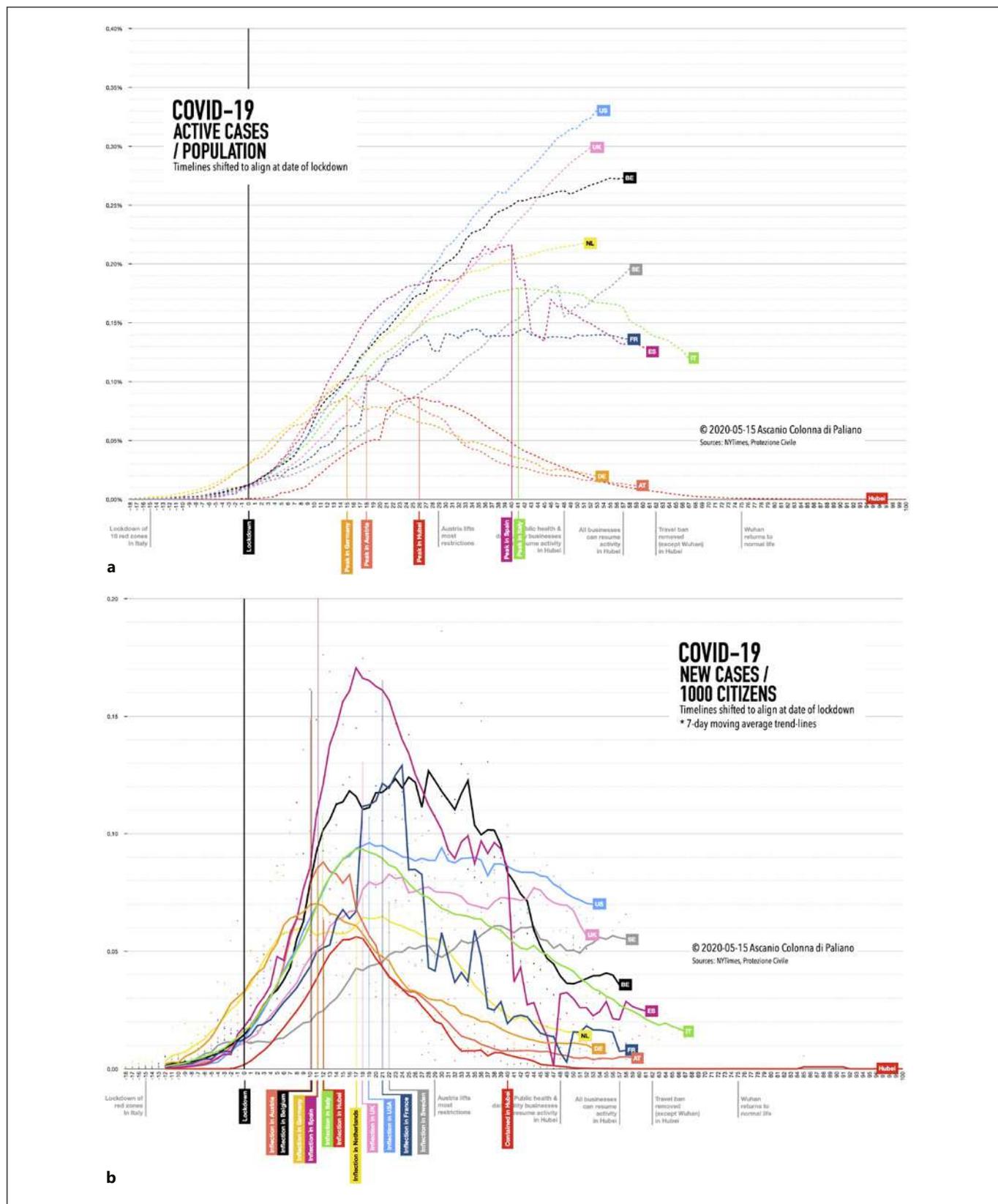
Fig. 1. a, **b** COVID-19 pandemic worldwide situation (updated to May 15, 2020).

Table 1. Risk factors for patients affected by SARS-CoV-2 infection

Risk factors	Reports	Sample size	Ref. No.
Aging and senescence	Median age of hospitalized patients: 49 years	41	13
	Median age of hospitalized patients: 51 years	201	4
	Median age of hospitalized patients: 56 years		
	Median age of hospitalized patients in ICU: 66 years	138	15
	Median age of hospitalized patients: 57 years	140	16
Smoking	Patients in progression: 27.3% smokers vs. 3% nonsmokers	76	26
Obesity and BMI	BMI of critical group 25.5 vs. 22.0 of noncritical group		
	Difference in lethality when BMI >25	112	33
	Risk of hospitalization in comparison with normal weight patients:		
	obese (OR 3.18), morbidly obese (OR 18.40)	4,778	36
DM	Risk of ARDS: 19% for patients with DM vs. 5.1% for patients without DM	201	4
	ICU/severe case with DM 11.7% vs. 4% without DM	1,527	41
	Comorbidities present in 48% of hospitalized patients		
	(most frequent hypertension followed by DM)	813	42
Inflammation and immune response	Blood parameters between severe and nonsevere cases	452	3
	$\quad$ C-reactive protein: 57.9 vs. 33.2 mg/L		
	$\quad$ NLR: 5.5 vs. 3.2		
	$\quad$ Leukocytes: 5.6 vs. 4.9×10^9/L		
	$\quad$ Lymphocytes: 0.8 vs. 1.0×10^9/L		
	Blood parameters between discharged and dead patients	150	50
	$\quad$ C-reactive protein: 34.1 vs. 126.6 mg/L		
	$\quad$ IL-6: 6.8 vs. 11.4 pg/mL		
	$\quad$ Platelet count: 222.1 vs. 173.6×10^9/L		
	$\quad$ White blood cells: 6.76 vs. 10.62×10^9/L		
	$\quad$ Lymphocytes: 1.42 vs. 0.60×10^9/L		
	Blood parameters between severe and nonsevere cases	30	51
	$\quad$ Platelet peak: 392 vs. 301×10^9/L		
	$\quad$ PLR: 626 vs. 262		

Method

We searched Medline/PubMed, Web of Science, Google Scholar and Cochrane library on March 19, 2020. Randomized controlled trials, systematic reviews, meta-analyses and case series describing SARS-CoV-2 and bladder cancer were identified. In particular, we focused our research on epidemiology, risk factors, biological process and therapeutic options. The following terms were the most commonly used: SARS-CoV-2, COVID-19, bladder cancer, risk factors, diabetes, obesity, aging, inflammation, cytokine, interleukin (IL), IL-6, smoking. There were no date or language restrictions on the search. References of relevant papers were searched manually for relevant studies. If more than one publication was identified from the same group, the most recent or complete one was included.

Two reviewers independently conducted the search, reviewed full texts and extracted data. The quality of included studies was assessed subjectively and classified as anecdotal, low, medium or high.

The search on Medline/PubMed, Web of Science, Google Scholar and Cochrane library identified 9,525 results in total. After

screening the abstracts, 95 papers were selected. After reading the full text, a further 32 were excluded leaving 64 to be included. Studies have been divided between those concerning cancer ($n = 44$) and those concerning COVID-19 ($n = 20$).

Results

Aging, Senescence and Comorbidities
COVID-19

Early research suggests that advanced age is a risk factor for severe laboratory-confirmed COVID-19 disease [13–16] (Tables 1, 2). One report by Huang et al. [13] reports a median age of COVID-19-related hospital admission of 49 years. Another interesting analysis focused on 201 hospitalized COVID-19 patients and reported that older age was associated with a higher risk of developing ARDS and that 52.4% of ARDS patients

Table 2. Risk factors for patients affected by high-risk non-muscle-invasive bladder cancer (NMIBC)

Risk factors	Reports	Sample size	Ref. No.
Aging and senescence	Bladder cancer mortality 15 times greater in individuals aged ≥65 years	–	17
Smoking	Bladder cancer patients: 33.9% current smokers, 46.8% former smokers and 17.4% nonsmokers Smokers are at increased risk for high-risk NMIBC than former and nonsmokers and dose response for the risk of a more aggressive cancer	1,859	30
	Risk of bladder cancer: former smokers (119.8/100,000 person-years), current smokers (177.3/100,000 person-years) and never smokers (39.8/100,000 person-years)	4,518,941	32
Obesity and BMI	Among NMIBC patients, 44.3% were obese with median BMI 29.2 Higher BMI associated with an increased risk of recurrences, progressions and mortality (all $p \leq 0.001$)	832	39
	Overweight and obesity associated with recurrences and progressions Addition of the BMI to a model that includes standard clinicopathological factors increases the C index by 9.9 for recurrences and 1.9 for progressions	1,155	40
DM	Among NMIBC patients, 37% had DM DM associated with recurrence-free survival and progression-free survival in both univariate and multivariate analysis	251	44
	Among NMIBC patients, 11.1% had DM 42.0% of patients had recurrence, 9.2% progression, 4.5% died; multivariable analysis reports that DM patients have a greater risk of recurrence and progression but when taking metformin the risk is lower	1,117	45
	Among NMIBC patients, 19.7% had DM Recurrences: 89.7% in patients with DM vs. 62.1% of non-DM patients Progressions: 38.1% in patients with DM vs. 28.2% of non-DM patients	1,172	46
Inflammation and immune response	A systemic inflammatory marker score was calculated based on NLR, PLR and LMR Recurrence-free survival 80.8, 47.35, 20.67 and 17.06% for patients with a systemic inflammatory marker score of 0, 1, 2 and 3 and progression free-survival 92.0, 75.67, 72.85 and 63.1%, respectively	1,155	57
	NLR predicts worse recurrence-free survival and progression-free survival	2,298	7
	Among NMIBC patients, 64.9% recurrences, 29.0% progressions and 14.3% deaths Basophil count associated with a 30% increment in the hazard of recurrence per unit increase of logarithmic basophil count	1,045	60
	NLR: 3.65±1.16 in BCG nonresponders and 2.61 ± 0.77 in BCG responders; NLR optimal cutoff ≥3 NLR correlates with recurrence and progression risk scores	100	61
	IL-6: 81±30.8 pg/mL in NMIBC patients vs 25.14±9.71 pg/mL in patients without NMIBC	85	56

died [4]. In this case the median age of hospitalized patients was 51 years. Bivariate Cox regression analysis confirmed that aging was a risk factor for ARDS and progression to death [4]. Wang et al. [14], on the other hand, described a higher median age of patients admitted to hospital (56 years old), and patients transferred to an ICU were even older, with a median age of 66 years. This increased risk of hospitalization, ARDS and mortality in older persons may be due in part to comorbidities. Comorbidities were reported to be more present in those treated in an ICU (72.2% of cases) and even in those who died (overall mortality 4.3%). Huang et al. [13] also reported that many hospitalized patients had underlying comorbidities. Older age was confirmed between worse prognosis risk factors in another group of 140 hospitalized patients who were on average 57 years old, and 64.3% of cases had underlying comorbidities [15]. Further, data from Italy suggest that a large proportion of COVID-19 patients who die have multiple pre-existing chronic conditions [16].

Bladder Cancer

Numerous demographic studies have shown that bladder cancer mortality is 15 times greater in individuals aged ≥65 years [17]. Aging is a multifactorial process observed in different organs that involves several cellular and molecular mechanisms. In particular, a structural alteration of the immune system can cause an inability to fight infections, decreased immune activation with vaccines and autoimmunity. Further, increased cancer progression may even be a consequence of a constitutive low-grade inflammation state. These changes can occur at a cellular level with impaired innate and adaptive immune cells and at the stromal microenvironment mainly on lymphoid organs [18]. A previous study described aging as a complex biological process that connects development and behavior of individual malignances with inflammation, immunosenescence, associated chronic diseases, extrinsic environment and psychosocial factors [19].

Senescence acts on the cell cycle because it is characterized by an arrest of cell proliferation that is reported when cells are under a potentially oncogenic stress. This arrest is considered irreversible because of lack of stimuli allowing cells to re-enter inside the cycle [20]. On the other hand, there are two major tumor suppressor pathways (p53/p21 and p16^{INK4a}/pRB) against malignant evolution [21]. In addition, chromatin compaction and gene expression change inside the cells causing the senescence-associated secretory phenotype with secretion of proinflammatory cytokines, chemokines, growth factors and proteases [22]. The microenvironment in which all these processes take place is permissive for initiation, development and progression of cancer. This evidence is in favor of degenerative pathology driving to hyperplasia, even evident in several xenograft studies [23]. The senescence-associated secretory phenotype in culture can also stimulate carcinogenesis that could evolve to epithelial-to-mesenchymal transition, a key point of the metastatic process [24]. Researchers from the Hebrew University of Israel described senescent cells as metabolically and transcriptionally active that secrete molecules continuously and as capable of altering the microenvironment through increased production of inflammatory mediators. It is a senescence-inflammatory effect that drives tumor proliferation feeding its progression mainly because their persistence promotes damage [25].

Smoking
COVID-19

Smoking has been described as a factor for poor COVID-19 disease evolution [26] (Tables 1, 2). As al-

ready reported, virus proteins support a strong interaction with human ACE2 followed by activation of immune system and inflammatory responses [2]. Smoking is considered to increase the expression of ACE2, a basic receptor leading to ARDS. It is possible that sex differences in hospitalization and mortality (more frequent in males) could partly be related to different smoking habits between males and females [27].

Liu et al. [26] divided 76 patients hospitalized for COVID-19 into an improved/stabilized group and a progression group. The progression group had a significantly higher history of smoking in comparison with others (27.3 vs. 3%). Multivariate logistic analysis confirmed that history of smoking, together with age, is a risk factor for disease progression. However, there is a lack of conclusive data in the literature regarding smoking and COVID-19 progression.

Bladder Cancer

Tobacco smoking is considered a risk factor for bladder cancer recurrence and progression. Smoking pattern, intensity and duration are responsible for poorer bladder cancer tumor features, and smoking is associated with a higher incidence of recurrences [28]. A recent paper on 1,859 patients affected by bladder cancer reported that 33.9% were current smokers, 46.8% former smokers and 17.4% nonsmokers. The authors found that smokers are at an increased risk of developing high-risk NMIBC than former and nonsmokers, and there is a statistically significant dose response for the risk of a more aggressive cancer type. However, this evidence is not completely supported by specific gene mutations [29]. On the other side a retrospective review conducted on 623 patients treated with BCG for high-grade NMIBC confirms, in both univariate and multivariate analyses, that smoking status is not associated with BCG response [30]. The bladder function is to store urine, and there is much time for carcinogens in the urine to affect the bladder. The carcinogens associated with smoking remain in contact with the genitourinary system until eliminated, thus a high rate of bladder cancer recurrences and progressions are reported among smokers [31, 32].

Obesity and Body Mass Index

COVID-19

Coronaviruses can cause more severe symptoms and complications in people with obesity-related conditions [33–36] (Tables 1, 2). A Chinese group conducted a retrospective analysis on 112 COVID-19 patients with car-

diovascular disease. They were divided into a critical group (admitted to the ICU) and a general group in accordance with the severity of the disease. Compared with the general group, the body mass index (BMI) of the critical group was significantly higher (average 22.0 vs. 25.5). After a further division into nonsurvivors and survivors, there was a statistically significant difference in survival between patients with a BMI >25 and those with a BMI <25 [33]. Several other studies found an association between obesity and worse viral influenza course, and between obesity and hospitalization due to influenza [34, 35]. A large trial with 4,778 participants suffering from influenza-like illness concluded that adults were more likely to be hospitalized if they were obese or morbidly obese compared to normal-weight people. Focusing the analysis on subjects who had an influenza secondary to coronavirus, once again, normal-weight participants were less likely to be hospitalized. The authors concluded that there is an increased risk of being hospitalized in adults, regardless of the viral pathogen status, depending on their weight [36].

Bladder Cancer

There is much evidence that correlates cancer and obesity. Weight, weight gain and obesity account for approximately 20% of all cancer cases, and there is evidence that cancer prognosis and survival are worse between obese people [37].

Biological mechanisms underlying the association between cancer and obesity are complex and include several different factors, such as increased secretion of steroid hormones, chronic high insulin levels, insulin resistance and a persistent inflammatory state [38].

Obesity is also recognized as a risk factor for poorer outcomes in bladder cancer as reported in a multicenter retrospective trial that included 892 patients with primary NMIBC treated with transurethral resection of the bladder with or without intravesical instillations. Univariate analysis confirmed that higher BMI and age were associated with a significantly increased risk of recurrences, progressions and cancer specific mortality. Multivariate analysis, adjusted for sex, concomitant carcinoma in situ, tumor size, number of tumors and intravesical therapy, reported that higher BMI and age remained independent predictors of recurrence, progression and cancer specific mortality [39]. An important trial on 1,155 patients affected by T1G3 NMIBC that underwent TURB followed by adjuvant instillation with BCG (induction and maintenance) found a statistically significant difference between obese and normal-weight patients in cancer recur-

rence and progression. Overweight and obesity were significantly associated with an increased risk of recurrence and progression after adjustment for classical clinicopathological parameters. In a model that included standard clinicopathological factors in addition to BMI, obesity increased the C index by 9.9 for recurrence and by 1.9 for progression. The authors concluded that obesity could have a relevant role in the management of T1G3 NMIBC if associated with obesity and that BMI should be taken into consideration at the initial diagnosis and when planning a therapeutic strategy [40].

DM and Other Comorbidities
COVID-19

Pneumonia, ARDS, end-organ failure and death are the most common complications of COVID-19 infection (Tables 1, 2), and those with underlying chronic comorbidities could be at higher risk of developing these conditions and having poorer outcomes [1]. One of the latest papers on the clinical characteristics of hospitalized patients affected by COVID-19 that included 201 subjects, ARDS was more frequent in those with comorbidities (especially hypertension and DM) [4]. An interesting meta-analysis reported that the COVID-19 pandemic spread as a disease mainly involving adults with comorbidities such as hypertension, diabetes and cardiocerebrovascular disease [1]. In particular, these comorbidities were strongly associated with poor prognosis. The heterogeneity test found that DM accounted for 11.7% of ICU/severe cases, but 4% of non-ICU/severe cases, although results were not statistically significant, possibly due to the small sample size. Even hypertension and cardiocerebrovascular disease were strongly and significantly associated with ICU/severe cases [41]. Another paper, published at the beginning of the epidemic, reports data of 813 hospitalized patients with exclusion of 600 individuals because they were still hospitalized at the moment of publication. Comorbidities were found in 48% of patients, with hypertension as the most common, followed by DM and coronary heart disease. The univariate analysis found a correlation between death and DM or coronary heart disease [42]. In a small case series, 64.7% of severe cases in patients developing pneumonia and ARDS showed one or more comorbidities, most commonly hypertension and DM [14, 15].

Bladder Cancer

In the literature there is much evidence suggesting a strong association between DM (mainly type 2) and cancer progression. One possible link is represented by hy-

perinsulinemia, hyperglycemia and fat-induced chronic inflammation [11]. On the other side there is some research suggesting an association between carcinogenesis and antidiabetic medications [43].

Hwang et al. [44] reported results from a trial of 251 patients treated with TURB who were divided into two groups in accordance with being affected or unaffected by DM at the time of surgery. Univariate analysis showed that DM was associated with recurrence-free and progression-free survival. Multivariate analysis also confirmed DM as an independent factor for recurrence and progression. Another association was found between DM and tumor multifocality and grade. Patients with diabetes were at a higher risk for recurrence and progression but for those taking metformin the risk decreased [45]. Another trial with a total of 1,172 patients affected by T1 high-grade NMIBC treated with TURB followed by maintenance BCG found that 19.7% of patients were affected by type 2 DM, and cancer recurrence was observed in 89.7% of these patients compared to 62.1% of patients without type 2 DM. Progression was seen in 38.1% of DM patients and 28.2% of non-DM patients. Evidence suggests that the hallmark of cancer evolution in DM patients is chronic inflammation caused by insulin, insulin-like growth factor-1, proinflammatory cytokines, oxidative stress and growth factor effects [46]. In particular, low-grade systemic inflammation, characteristic of type 2 DM, could favor initiation and progression of bladder cancer. At the moment the role of immune cells for bladder cancer pathogenesis is under evaluation. In particular, a protumor effect has been attributed to the innate immune system while the adaptive immune system seems to play an antitumor effect [5–47].

Inflammation and Immune System Response
COVID-19
Immune response together with inflammation is essential to control and eliminate coronavirus infection (Tables 1, 2). Our role is to exactly understand the interaction between COVID-19 and the immune system, to clarify the course of inflammation, understand cytokine storm liberation and avoid the major damage occurring to our lungs and preserve health. The immune system develops an innate response through detection of viral pathogen using pattern recognition receptors including Toll-like receptors, retinoic acid-inducible gene-I-like, nucleotide-binding oligomerization domain-like receptor, C-type lectin-like receptor and free-molecule receptors. Even interferons, dendritic cells and defensins play a role in the innate response. The adaptive immune response is acted by T cells (mainly CD4+ and CD8+), humoral and antibody response [2]. The typical presentation of severe cases of SARS-CoV-2-infected patients is with lymphopenia, neutrophilia, high neutrophil-to-lymphocyte ratio and lower monocytes, eosinophils and basophils [3]. Furthermore, high infection-related biomarkers such as procalcitonin, erythrocyte sedimentation rate, serum ferritin and C-reactive protein are reported [3]. The cytokine storm is another typical process related to inflammation and immune response; tumor necrosis factors, IL-2R, IL-6, IL-8 and IL-10 are delivered in the blood stream. Severe COVID-19 cases commonly have T lymphopenia (mainly CD4+) and increased neutrophils [3]. In these cases, NLR, an important item to evaluate systemic inflammation and infection, is reported to be very high and could be used as a marker to understand disease course and to identify those patients who have a higher risk to evolve to ARDS or death [48]. Cytokines and chemokines, on the other side, play an important role for immunity and inflammation during infection and are, as well, related to adverse outcomes [49]. A retrospective multicenter study with 150 patients affected by COVID-19 found that elevated ferritin and IL-6 are predictors of mortality, suggesting that mortality might be due to virally driven hyperinflammation [50]. Another group of researchers screened 30 hospitalized patients for COVID-19 excluding those with chronic diseases and found that the average platelet peak during the treatment of severely affected patients was significantly higher than in non-severely affected ones, and the platelet-to-lymphocyte ratio (PLR) as well was on average triple in severe cases. Multivariate analysis confirms that platelet peak and PLR were influencing factors in severe cases. Mature megakaryocytes in the bone marrow produce platelets. Inflammation response with cytokine storm (thyroid peroxidase, IL-3, IL-6, IL-9, IL-11) and stem cell factor can promote the production of megakaryocytes. For this reason, lymphocytes and platelet level, together with PLR, can be used as a marker reflecting body infections and inflammation. Once again inflammation, immune response and cytokine storm are essential for understanding COVID-19 patients with poor prognosis and higher death risk [51].

Bladder Cancer
The role of inflammation in cancer is increasingly studied to help understand mechanisms such carcinogenesis, resistance, progression and metastasis. Neutrophils, part of the innate immune system, play a primary role in resistance against extracellular pathogens and in-

flammation. In the tumor, microenvironment stimulation of the immune system takes place; increases in host components, growing blood vessels and inflammatory infiltrates are reported [52]. In addition, cytokines released by the tumor microenvironment have a pivotal role in the development and progression of bladder cancer. Between inflammatory cytokines, IL-6 is proinflammatory and produced by various cells. There is evidence showing how IL-6 plays a crucial role in cancer development, progression and metastasis by regulating the tumor microenvironment and cancer stem cells [53]. For different cancers, including bladder cancer, the IL-6/Janus kinase (JAK)/STAT3 pathway is hyperactivated, and this is generally a poor prognostic signal. In the tumor microenvironment, the IL-6/JAK/STAT3 axis acts suppressing the antitumor immune response and on the other side facilitating proliferation, survival, invasiveness and metastasis of tumor cells [54]. IL-6 acts directly on tumor cells to induce the expression of STAT3 target genes, which encode proteins that drive tumor proliferation and/or survival [55]. A group of researchers measured mean IL-6 levels in urine samples from patients with NMIBC (81 ± 30.8 pg/mL), which were slightly higher than those without malignant disease (25.14 ± 9.71 pg/mL) [56].

Alterations in neutrophils, lymphocytes and platelets accompany the systemic inflammatory response to cancer, and the NLR has been recognized as a factor related to poor prognosis for many solid tumors, including bladder cancer [57]. Cantiello et al. [58] conducted a trial on 1,155 patients with high-risk NMIBC, and they calculated a systemic inflammatory marker score based on cutoffs for the NLR, PLR and lymphocyte-monocyte ratio. Results showed that systemic inflammatory marker scores 1, 2 and 3 were associated with higher recurrence and progression rates, and results confirm a relation with worse outcomes even when adjusted for pathological variables such as tumor size, carcinoma in situ and multifocality. A systematic meta-analysis on the role of the NLR in patients with NMIBC undergoing surgery with TURB has been conducted. Six studies and 2,298 patients included in the analysis showed that worse recurrence-free survival and worse progression-free survival were associated with high NLR blood levels. Even considering patients treated with BCG immunotherapy, the NLR was an independent predictor of recurrence and progression [7]. The immune system plays an antagonist role in the pathogenesis of bladder cancer, considered a highly immunogenic malignancy with a strong mutagenic rate [47]. The adaptive immune system has an antitumor effect while the innate system has a protumor effect. When

investigating the role of NLR in cancer development and aggression, the increased number of neutrophils that interact with other cell populations responsible for the production of cytokines and effector molecules should be noted [52]. Even the microenvironment plays an important role for correct neutrophil function, considering their recruitment to mediate host defense through a variety of signals including chemokines, lipid mediators and pathogen signals [59]. On the other hand, protumor activities include extracellular matrix remodeling, cell invasion, metastasis, angiogenesis, cancer cell proliferation, lymphangiogenesis and inhibition of the antitumoral immune surveillance [60]. A further trial reported an association between basophil count and time to recurrence in NMIBC patients treated with BCG. In fact, the multivariate analysis on a total of 1,045 patients showed that logarithmic transformation of basophil count was associated with a 30% increase in the risk of recurrence per unit increase of logarithmic basophil count [61]. BCG response has been evaluated by Racioppi et al. [62] on 100 high-risk NMIBC patients. They reported an optimal cutoff for NLR ≥3 and a mean NLR value of 3.65 ± 1.16 for BCG nonresponders and 2.61 ± 0.77 for BCG responders. They concluded that the NLR correlated with recurrence and progression risk scores, and in multivariate analysis, the NLR was associated with bladder cancer evolution.

Cancer and Increased COVID-19 Prevalence

Zhang et al. [63] retrospectively analyzed 28 patients affected by cancer who developed SARS-CoV-2 infection. They reported a mortality (28.6%) 10 times higher than all other COVID-19 patients in China and noted that recent use of anticancer therapies was an independent predictor of death or severe complications. Interestingly, even patients already in the hospital for cancer treatment were at a higher risk of developing COVID-19. Patients with cancer could have a poorer prognosis and higher risk of SARS-CoV-2 infection compared with those without cancer because immunosuppression could be caused by the tumor and anticancer treatments [64]. Furthermore, the risk of severe events has been reported as higher for cancer patients and even higher for patients undergoing treatments like chemotherapy [65]. A recent paper reports that overwhelming inflammation and cytokine-associated injury during cancer could be important in facilitating severe events in patients with COVID-19. On the other side, there is evidence showing how cancer development is usually associated with a blunted immune status characterized by overexpression of immunosuppressive cytokines, suppressed induction of proinflam-

matory danger signals, impaired dendritic cell maturation, and enhanced functional immunosuppressive leukocyte populations. This cascade of events is in contradiction to what is believed to result in severe complications in patients with COVID-19 [66].

In conclusion, reported data are not sufficient to conclude that patients with cancer have a higher risk of COVID-19. Currently only small case studies with several heterogeneities (different cancer types, highly variable disease courses and uncommon treatment strategies) are available; thus, it is difficult to draw final conclusions. More well-conducted analyses of the association between cancer and COVID-19 are expected in the upcoming months/years.

Other Urological Malignancies and COVID-19

ACE2 expression is organ-specific, and its distribution is mainly in the kidney, male testis, and cardiovascular and gastrointestinal systems.

ACE2 expression is correlated with an increased survival rate in renal and liver cancer; thus, it could even be a prognostic marker. While ACE2 is a functional receptor for COVID-19, it has a potential antitumor role in cancer [67], especially in kidney cancer.

Prostate cancer is regulated by androgen receptors that are related to transcription of the transmembrane protease serine 2, which is required for SARS-CoV-2 because it primes the spike protein of the virus [68]. A group of researchers extracted data regarding 4,532 males with confirmed SARS-CoV-2 infection and found that prostate cancer patients receiving androgen deprivation therapy had a significantly lower risk of infection compared to patients who did not receive androgen deprivation therapy [69].

In conclusion, androgen sensitivity is a determinant for COVID-19 disease severity, and even gender incidence of COVID-19 and cancer are probably related to androgens and ACE2 expression. Even if studies are still needed before making epidemiological conclusions, recognizing the importance of androgens may offer another targeted therapy for trials, with androgen suppression to reduce host vulnerability [70].

Conclusion

Worldwide we are facing a fast demographic shift toward an increasingly aging population, which brings several changes to the social, economic, political and, particularly, medical fields. COVID-19 is a pandemic, and all countries worldwide are fighting against it. Currently, Italy is one of the most affected countries, and the Italian population demographic characteristics (approx. 23% of people are aged 65 years or older) could partly explain the higher case-fatality rates [17]. This novel disease can affect anyone, although people at higher risk of negative outcomes such as ARDS and death are often older persons with comorbidities such as diabetes, hypertension or coronary artery disease. Even obesity and smoking have been suggested as risk factors for a worse prognosis. However, considering the fact that this is a novel problem, current data need to be confirmed by further, larger studies on diverse populations to provide more concrete evidence. Bladder cancer, on the other hand, is a well-known disease that has been studied for a longer period, and it shares some prognostic risk factors, including aging, obesity, smoking and comorbidities (DM in particular). Evidence in this case is stronger but still far from being fully confirmed.

Inflammation is considered to be one of the hallmarks of cancer, and approximately 20% of tumors progress because of chronic inflammation [26]. Immune system response, as well, is a major player in carcinogenesis, cancer progression and metastasis processes. Innate and adaptive immune response are involved during bladder cancer. Prognosis and sensitivity to treatment of bladder cancer are related to tumor-infiltrating immune cells, and understanding the immune response could be the starting point for the development of personalized therapy and precision medical treatments [71].

A similar interplay between inflammation and immune response is reported during SARS-CoV-2 infection. The cytokine storm, including interleukins and tumor necrosis factors, is part of the inflammation and immune system activation reported in both diseases. There are several inflammatory mediators (e.g., tumor necrosis factor α, IL-6 and IL-17) facilitating chronic inflammation and leading to decreased antitumor immunity with faster tumor progression. This status could facilitate COVID-19 with respiratory distress and accelerate cancer progression, increasing the risk of mortality of patients affected by most common uro-oncological tumors like bladder cancer. The innate immune system is important for the fight against bladder cancer but more importantly against viruses including SARS-CoV-2 [72].

All these prognostic risk factors are reported not only for bladder cancer and are common with several solid tumors (including breast, colorectal, prostate cancers, etc.). Cancer progression can be exacerbated by inflammation and infections while the microenvironment is

important for offering the correct place for tumorigenesis. The link between them and the immune system is mediated by the cytokines produced from innate immune cells that stimulate tumor growth and progression [73]. For this reason, it is important to understand all these mechanisms in order to find new therapies and strategies to block infection and cancer progression. Further than commonly used therapies, controlling cytokine production and the inflammatory response is promising.

Agents targeting IL-6, the IL-6 receptor or JAKs are already used for the treatment of inflammatory conditions or myeloproliferative neoplasms. Elevated levels of IL-6 are observed in chronic inflammatory conditions, such as rheumatoid arthritis and inflammatory bowel disease and in a large number of patients with hematopoietic malignancies or solid tumors [57]. Inhibition of tumor cell growth and stimulation of antitumor immunity are promising treatments that target the IL-6/JAK/STAT3 pathway in patients with cancer. Novel inhibitors of the IL-6/JAK/STAT3 pathway, including STAT3-selective inhibitors, are under analysis, and the combination of these inhibitors with currently approved therapeutic agents directed against immune-checkpoint inhibitors could offer other possibilities [54]. Different monoclonal antibodies for anti-IL-6/IL-6 receptor therapy, such as siltuximab, have shown potential benefits toward cancers either as a single agent or in combination with other agents. Another anti-IL-6, tocilizumab, commonly used for rheumatoid arthritis, offers promising results for treating cancer, particularly when combined with conventional drugs. Another association that may be helpful to improve immunotherapy of cancer is the link between IL-6-blocking agents and epidermal growth factor receptor inhibitors or other targeted therapy [47, 52, 54–62, 64]. Therefore, the IL-6-signaling pathway represents an attractive target for therapeutic or preventive interventions, not only for cancer, but even for infectious diseases and chronic inflammatory diseases. Few multicenter randomized controlled trials, still unpublished, are in progress for tocilizumab in patients with COVID-19 pneumonia considering that elevated IL-6 and JAK inhibition could affect both inflammation and cellular viral entry of SARS-CoV-2.

Another possible common target could be IL-4 that inhibits SARS-CoV-2 replication partly through downregulation of ACE2, and this role could be speculated even for SARS-CoV-2 infection [74]. In contrast, IL-4 is overexpressed in bladder cancer and could have a role as prognostic biomarker and as therapeutic target [75].

BCG, which has long been used as an adjuvant therapy for high-risk NMIBC, has been proposed recently as another possible strategy for COVID-19. Mandated BCG vaccination patients can have a different response against COVID-19 [76]. On a recent update, de Vrieze [77] reports that researchers started testing whether a century-old vaccine against tuberculosis can stimulate the human immune system in a broad way, allowing it to better fight SARS-CoV-2 and, perhaps, prevent infection. Comparing COVID-19 daily incidence between countries with or without BCG vaccination there is a strong difference: 0.8 versus 34.8 per million, respectively. This report hypothesizes a potential expansion of memory T lymphocytes and B lymphocytes that can combat future exposures [78]. This also reaffirms the role of the innate immune system that can develop memory and could play a vital role against bladder cancer and viral infections.

A universal vaccine may be the best solution to control the COVID-19 pandemic but unfortunately it will take a long time to be developed, so alternative therapeutic measures could be directed toward the innate immune response and inflammation. Vaccines are promising even for some cancers, and those that have been developed offer an optimal protection.

Disclosure Statement

The authors have nothing to disclose.

Author Contributions

Conception or design of the work: Matteo Ferro, Gina Maria Busetto, Alessandro Sciarra. *Acquisition of data:* Gian Maria Busetto, Francesco Del Giudice, Martina Maggi. *Interpretation of data for the work:* Giuseppe Lucarelli, Gennaro Musi, Katie Palmer, Ascanio Colonna di Paliano. *Drafting the paper:* Gian Maria Busetto, Daniele D'Agostino, Daniele Romagnoli. *Paper critically revising:* Ettore De Berardinis, Ottavio De Cobelli, Matteo Muto, Angelo Porreca, Katie Palmer, Rodolfo Hurle, Daniela Terracciano.

References

1 Li LQ, Huang T, Wang YQ, Wang ZP, Liang Y, Huang TB, et al. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. J Med Virol. 2020 Mar; 2020(Mar):12. [Epub ahead of print].

2 Li G, Fan Y, Lai Y, Han T, Li Z, Zhou P, et al. Coronavirus infections and immune responses. J Med Virol. 2020 Apr;92(4):424–32.

3 Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis. 2020 Mar;ciaa248. Epub.

4 Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020 Mar; DOI: 10.1001/jamainternmed.2020.0994. Epub.

5 Babjuk M, Böhle A, Burger M, Capoun O, Cohen D, Compérat EM, et al. EAU Guidelines on Non-Muscle-invasive Urothelial Carcinoma of the Bladder: Update 2016. Eur Urol. 2017 Mar;71(3):447–61.

6 Nicolazzo C, Busetto GM, Gradilone A, Sperduti I, Del Giudice F, Loreni F, et al. Circulating Tumor Cells Identify Patients with Super-High-Risk Non-Muscle-Invasive Bladder Cancer: Updated Outcome Analysis of a Prospective Single-Center Trial. Oncologist. 2019 May;24(5):612–6.

7 Vartolomei MD, Porav-Hodade D, Ferro M, Mathieu R, Abufaraj M, Foerster B, et al. Prognostic role of pretreatment neutrophil-to-lymphocyte ratio (NLR) in patients with non-muscle-invasive bladder cancer (NMIBC): A systematic review and meta-analysis. Urol Oncol. 2018 Sep;36(9):389–99.

8 Diakos CI, Charles KA, McMillan DC, Clarke SJ. Cancer-related inflammation and treatment effectiveness. Lancet Oncol. 2014 Oct; 15(11):e493–503.

9 Rajwa P, Życzkowski M, Paradysz A, Bujak K, Bryniarski P. Evaluation of the prognostic value of LMR, PLR, NLR, and dNLR in urothelial bladder cancer patients treated with radical cystectomy. Eur Rev Med Pharmacol Sci. 2018 May;22(10):3027–37.

10 Tang X, Du P, Yang Y. The clinical use of neutrophil-to-lymphocyte ratio in bladder cancer patients: a systematic review and meta-analysis. Int J Clin Oncol. 2017 Oct;22(5):817–25.

11 Ferro M, Katalin MO, Buonerba C, Marian R, Cantiello F, Musi G, et al. Type 2 diabetes mellitus predicts worse outcomes in patients with high-grade T1 bladder cancer receiving bacillus Calmette-Guérin after transurethral resection of the bladder tumor. Urol Oncol. 2020 May;38(5):459–64. Epub ahead of print.

12 Bottazzi B, Riboli E, Mantovani A. Aging, inflammation and cancer. Semin Immunol. 2018 Dec;40:74–82.

13 Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb;395(10223):497–506.

14 Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020 Feb;323(11):1061. Epub ahead of print.

15 Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020 Feb;all.14238. Epub.

16 Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA. 2020 Mar; DOI: 10.1001/jama.2020.4683. Epub.

17 Messing EM. Urothelial tumors of the bladder. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, editors. Campbell-Walsh Urology. 9th ed. Philadelphia: Saunders-Elsevier; 2008. Chapt 75, p. 2407–46.

18 Sadighi Akha AA. Aging and the immune system: an overview. J Immunol Methods. 2018 Dec;463:21–6.

19 Zhang X, Meng X, Chen Y, Leng SX, Zhang H. The Biology of Aging and Cancer: Frailty, Inflammation, and Immunity. Cancer J. 2017 Jul/Aug;23(4):201–5.

20 Campisi J, d'Adda di Fagagna F. Cellular senescence: when bad things happen to good cells. Nat Rev Mol Cell Biol. 2007 Sep;8(9): 729–40.

21 Beauséjour CM, Krtolica A, Galimi F, Narita M, Lowe SW, Yaswen P, et al. Reversal of human cellular senescence: roles of the p53 and p16 pathways. EMBO J. 2003 Aug;22(16): 4212–22.

22 Campisi J. Aging, cellular senescence, and cancer. Annu Rev Physiol. 2013;75(1):685–705.

23 Liu D, Hornsby PJ. Senescent human fibroblasts increase the early growth of xenograft tumors via matrix metalloproteinase secretion. Cancer Res. 2007 Apr;67(7):3117–26.

24 Laberge RM, Awad P, Campisi J, Desprez PY. Epithelial-mesenchymal transition induced by senescent fibroblasts. Cancer Microenviron. 2012 Apr;5(1):39–44.

25 Lasry A, Ben-Neriah Y. Senescence-associated inflammatory responses: aging and cancer perspectives. Trends Immunol. 2015 Apr; 36(4):217–28.

26 Liu W, Tao ZW, Wang L, Yuan ML, Liu K, Zhou L, et al. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. Chin Med J (Engl). 2020 May;133(9):1032–8.

27 Cai H. Sex difference and smoking predisposition in patients with COVID-19. Lancet Respir Med. 2020 Apr;8(4):e20. ; Epub ahead of print.

28 Soria F, Marra G, Čapoun O, Soukup V, Gontero P. Prevention of bladder cancer incidence and recurrence: tobacco use. Curr Opin Urol. 2018 Jan;28(1):80–7.

29 Barbosa AL, Vermeulen SH, Aben KK, Grotenhuis AJ, Vrieling A, Kiemeney LA. Smoking intensity and bladder cancer aggressiveness at diagnosis. PLoS One. 2018 Mar; 13(3):e0194039.

30 Sfakianos JP, Shariat SF, Favaretto RL, Rioja J, Herr HW. Impact of smoking on outcomes after intravesical bacillus Calmette-Guérin therapy for urothelial carcinoma not invading muscle of the bladder. BJU Int. 2011 Aug; 108(4):526–30.

31 Turner B, Drudge-Coates L. Bladder cancer: risk factors, diagnosis and treatment. Cancer Nurse Practice. 2012;11(7):30–6.

32 Freedman ND, Silverman DT, Hollenbeck AR, Schatzkin A, Abnet CC. Association between smoking and risk of bladder cancer among men and women. JAMA. 2011 Aug; 306(7):737–45.

33 Peng YD, Meng K, Guan HQ, Leng L, Zhu RR, Wang BY, et al. [Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nCoV]. Zhonghua Xin Xue Guan Bing Za Zhi. 2020 Mar; 48(0):E004. Epub. Chinese.

34 Martin ET, Archer C, McRoberts J, Kulik J, Thurston T, Lephart P, et al. Epidemiology of severe influenza outcomes among adult patients with obesity in Detroit, Michigan, 2011. Influenza Other Respir Viruses. 2013 Nov; 7(6):1004–7.

35 Cocoros NM, Lash TL, DeMaria A Jr, Klompas M. Obesity as a risk factor for severe influenza-like illness. Influenza Other Respir Viruses. 2014 Jan;8(1):25–32.

36 Moser JS, Galindo-Fraga A, Ortiz-Hernández AA, Gu W, Hunsberger S, Galán-Herrera JF, et al.; La Red ILI 002 Study Group. Underweight, overweight, and obesity as independent risk factors for hospitalization in adults and children from influenza and other respiratory viruses. Influenza Other Respir Viruses. 2019 Jan;13(1):3–9.

37 Wolin KY, Carson K, Colditz GA. Obesity and cancer. Oncologist. 2010;15(6):556–65.

38 Ferro M, Terracciano D, Buonerba C, Lucarelli G, Bottero D, Perdonà S, et al. The emerging role of obesity, diet and lipid metabolism in prostate cancer. Future Oncol. 2017 Feb;13(3):285–93.

39 Kluth LA, Xylinas E, Crivelli JJ, Passoni N, Comploj E, Pycha A, et al. Obesity is associated with worse outcomes in patients with T1 high grade urothelial carcinoma of the bladder. J Urol. 2013 Aug;190(2):480–6.

40 Ferro M, Vartolomei MD, Russo GI, Cantiello F, Farhan AR, Terracciano D, et al. An increased body mass index is associated with a worse prognosis in patients administered BCG immunotherapy for T1 bladder cancer. World J Urol. 2019 Mar;37(3):507–14.

41 Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol. 2020 May;109(5):531–8. ; Epub ahead of print.

42 Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 Mar 11; pii: S0140-6736(20)30566-3. DOI: 10.1016/S0140-6736(20)30566-3. Epub.

43 Wojciechowska J, Krajewski W, Bolanowski M, Kręcicki T, Zatoński T. Diabetes and Cancer: a Review of Current Knowledge. Exp Clin Endocrinol Diabetes. 2016 May;124(5):263–75.

44 Hwang EC, Kim YJ, Hwang IS, Hwang JE, Jung SI, Kwon DD, et al. Impact of diabetes mellitus on recurrence and progression in patients with non-muscle invasive bladder carcinoma: a retrospective cohort study. Int J Urol. 2011 Nov;18(11):769–76.

45 Rieken M, Xylinas E, Kluth L, Crivelli JJ, Chrystal J, Faison T, et al. Association of diabetes mellitus and metformin use with oncological outcomes of patients with non-muscle-invasive bladder cancer. BJU Int. 2013 Dec;112(8):1105–12.

46 Shadpour P, Zamani M, Aghaalikhani N, Rashtchizadeh N. Inflammatory cytokines in bladder cancer. J Cell Physiol. 2019 Feb; 234(9):14489–99. ; Epub ahead of print.

47 Thompson DB, Siref LE, Feloney MP, Hauke RJ, Agrawal DK. Immunological basis in the pathogenesis and treatment of bladder cancer. Expert Rev Clin Immunol. 2015 Feb; 11(2):265–79.

48 Curbelo J, Luquero Bueno S, Galván-Román JM, Ortega-Gómez M, Rajas O, Fernández-Jiménez G, et al. Inflammation biomarkers in blood as mortality predictors in community-acquired pneumonia admitted patients: importance of comparison with neutrophil count percentage or neutrophil-lymphocyte ratio. PLoS One. 2017 Mar;12(3):e0173947.

49 Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol. 2017 Jul; 39(5):529–39.

50 Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020 May;46(5):846–8. Epub.

51 Qu R, Ling Y, Zhang YH, Wei LY, Chen X, Li XM, et al. Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19. J Med Virol. 2020 Mar;jmv.25767. Epub.

52 Galdiero MR, Bonavita E, Barajon I, Garlanda C, Mantovani A, Jaillon S. Tumor associated macrophages and neutrophils in cancer. Immunobiology. 2013 Nov;218(11):1402–10.

53 Hong DS, Angelo LS, Kurzrock R. Interleukin-6 and its receptor in cancer: implications for translational therapeutics. Cancer. 2007 Nov;110(9):1911–28.

54 Johnson DE, O'Keefe RA, Grandis JR. Targeting the IL-6/JAK/STAT3 signalling axis in cancer. Nat Rev Clin Oncol. 2018 Apr;15(4): 234–48.

55 Goulet CR, Champagne A, Bernard G, Vandal D, Chabaud S, Pouliot F, et al. Cancer-associated fibroblasts induce epithelial-mesenchymal transition of bladder cancer cells through paracrine IL-6 signalling. BMC Cancer. 2019 Feb;19(1):137.

56 Chen MF, Lin PY, Wu CF, Chen WC, Wu CT. IL-6 expression regulates tumorigenicity and correlates with prognosis in bladder cancer. PLoS One. 2013 Apr;8(4):e61901.

57 Lucca I, Jichlinski P, Shariat SF, Rouprêt M, Rieken M, Kluth LA, et al. The neutrophil-to-lymphocyte ratio as a prognostic factor for patients with urothelial carcinoma of the bladder following radical cystectomy: validation and meta-analysis. Eur Urol Focus. 2016 Apr; 2(1):79–85.

58 Cantiello F, Russo GI, Vartolomei MD, Farhan AR, Terracciano D, Musi G, et al. Systemic Inflammatory Markers and Oncologic Outcomes in Patients with High-risk Non-muscle-invasive Urothelial Bladder Cancer. Eur Urol Oncol. 2018 Oct;1(5):403–10.

59 Kruger P, Saffarzadeh M, Weber AN, Rieber N, Radsak M, von Bernuth H, et al. Neutrophils: between host defence, immune modulation, and tissue injury. PLoS Pathog. 2015 Mar;11(3):e1004651.

60 Mantovani A, Cassatella MA, Costantini C, Jaillon S. Neutrophils in the activation and regulation of innate and adaptive immunity. Nat Rev Immunol. 2011 Jul;11(8):519–31.

61 Ferro M, Di Lorenzo G, Vartolomei MD, Bruzzese D, Cantiello F, Lucarelli G, et al. Absolute basophil count is associated with time to recurrence in patients with high-grade T1 bladder cancer receiving bacillus Calmette-Guérin after transurethral resection of the bladder tumor. World J Urol. 2020 Jan;38(1): 143–50.

62 Racioppi M, Di Gianfrancesco L, Ragonese M, Palermo G, Sacco E, Bassi PF. Can Neutrophil-to-Lymphocyte ratio predict the response to BCG in high-risk non muscle invasive bladder cancer? Int Braz J Urol. 2019 Mar-Apr;45(2):315–24.

63 Zhang L, Zhu F, Xie L, et al. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. Ann Oncol. 2020 Mar 26; pii: S0923-7534(20)36383-3. DOI: 10.1016/j.annonc.2020.03.296. Epub.

64 Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020 Mar;21(3):335–7.

65 Xia Y, Jin R, Zhao J, Li W, Shen H. Risk of COVID-19 for patients with cancer. Lancet Oncol. 2020 Apr;21(4):e180.

66 Rossi JF, Lu ZY, Jourdan M, Klein B. Interleukin-6 as a therapeutic target. Clin Cancer Res. 2015 Mar;21(6):1248–57.

67 Fu J, Zhou B, Zhang L, Balaji KS, Wei C, Liu X, et al. Expressions and significances of the angiotensin-converting enzyme 2 gene, the receptor of SARS-CoV-2 for COVID-19. Mol Biol Rep. 2020 May; DOI: 10.1007/s11033-020-05478-4. Epub.

68 Wambier CG, Goren A, Vaño-Galván S, Ramos PM, Ossimetha A, Nau G, et al. Androgen sensitivity gateway to COVID-19 disease severity. Drug Dev Res. 2020 May;ddr.21688. Epub.

69 Montopoli M, Zumerle S, Vettor R, et al. Androgen-deprivation therapies for prostate cancer and risk of infection by SARS-CoV-2: a population-based study (n = 4532). Ann Oncol. 2020 May 4; pii:S0923-7534(20)39797-0. DOI: 10.1016/j.annonc.2020.04.479. Epub.

70 Wambier CG, Goren A. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is likely to be androgen mediated. J Am Acad Dermatol. 2020 Apr 10; pii: S0190-9622(20)30608-3. DOI: 10.1016/j.jaad.2020.04.032. Epub.

71 Wu Z, Zhu K, Liu Q, Liu Y, Chen L, Cui J, et al. Profiles of Immune Infiltration in Bladder Cancer and its Clinical Significance: an Integrative Genomic Analysis. Int J Med Sci. 2020 Mar;17(6):762–72.

72 Daza J, Charap A, Wiklund PN, et al. Role of the innate immune system in the development, progression, and therapeutic response of bladder cancer. Eur Urol Focus. 2020 Feb 25; pii: S2405-4569(20)30070-5. DOI: 10.1016/j.euf.2020.02.013. Epub.

73 Lin WW, Karin M. A cytokine-mediated link between innate immunity, inflammation, and cancer. J Clin Invest. 2007 May;117(5):1175–83.

74 de Lang A, Osterhaus AD, Haagmans BL. Interferon-gamma and interleukin-4 downregulate expression of the SARS coronavirus receptor ACE2 in Vero E6 cells. Virology. 2006 Sep;353(2):474–81.

75 Joshi BH, Leland P, Lababidi S, Varrichio F, Puri RK. Interleukin-4 receptor alpha overexpression in human bladder cancer correlates with the pathological grade and stage of the disease. Cancer Med. 2014 Dec;3(6):1615–28.

76 Berg MK, Yu Q, Salvador CE, et al. Mandated bacillus Calmette-Guérin (BCG) vaccination predicts flattened curves for the spread of COVID-19. medRxiv Preprints. DOI: 10.1101/2020.04.05.20054163.

77 de Vrieze J. Can a century-old TB vaccine steel the immune system against the new coronavirus? Science. 2020 Mar; DOI: 10.1126/science.abb8297. Available from: https://www.sciencemag.org

78 Hegarty PK, Sfakianos JP, Giannarini G, DiNardo AR, Kamat AM. COVID-19 and Bacillus Calmette-Guérin: what is the Link? Eur Urol Oncol. Forthcoming 2020 Apr;S2588-9311(20)30049-3.