

Is COVID-19 impacting prostate cancer screening? A survey of prostate-specific antigen test requests during a local outbreak

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ABSTRACT

Background

Although the ongoing pandemic of coronavirus disease 2019 (COVID-19) is directly contributing to negatively affect global health and fitness, the restrictive measures applied for containing the outbreaks are also impacting detection and management of many diseases, including cancers. This study aimed to establish if and how the COVID-19 outbreak may have impacted the practice of routine prostate cancer screening in Verona, Italy.

Methods

We searched the laboratory information system of the Service of Laboratory Medicine of the University Hospitals of Verona to identify all test requests for total prostate-specific antigen (PSA) and vitamin D (Vit D);

i.e., the locally most requested immunochemical test) for outpatients during the last five years (December 10, 2016, to December 10, 2020). The weekly requests for these tests placed between February 25 and December 9, 2020, were compared to those placed during the same period of previous four years (i.e., 2016-2019).

Results

The volume of test requests for both Vit D and PSA did not differ in 2020 compared to previous four years. However, a dramatic decline was observed during the local lockdown period (between March 10 and May 17, 2020), with median decrease of 76% for Vit D and 62% for total PSA, respectively. This reduction was compensated by 13% increase for Vit D and 43% increase for total PSA in post-lockdown period.

Conclusion

These results show that the lockdown period established during the first peak of the COVID-19 outbreak in Italy's Verona province was associated with a dramatic decrease in routine prostate cancer screenings.



INTRODUCTION

Evidence now clearly attests that the ongoing coronavirus disease 2019 (COVID-19) pandemic is not only directly causing unprecedented morbidity and mortality around the world, but its continuous and virtually unstoppable spread is also influencing detection and management of many other acute and chronic diseases [1,2]. The potential consequences to global health is multifaceted, as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection exacerbates pre-existing diseases such as cancer, diabetes, cardiovascular disease, etc., leading to increased morbidity and mortality in such infected patients. Moreover, the continuous restrictions

are consistently limiting access to primary and secondary care, thus potentially causing diagnostic delays, underdiagnosis and undertreatment of non-COVID-19-related illnesses [3]. Many warning signals have been raised on observed decreases in care for routine pathologies during the pandemic, for example, hospitalizations for acute myocardial infarction were considerably decreased during the first wave of the outbreak [4-7].

Similar evidence has been provided with respect for general [8], emergency [9] and trauma surgery utilization [10], the diagnosis and therapeutic management of diabetes [11] and cancer [12], along with many other severe or life-threatening conditions [13], with pediatric care being no exception [14]. The widespread public avoidance of hospitals and delay in seeking routine medical care during the pandemic is likely translating into a large burden of underdiagnosis, with missed opportunities to provide timely and appropriate treatments, consequently leading to increased out-of-hospital chronic disability and mortality.

Prostate cancer is the third most frequently diagnosed malignant disease worldwide, the second in the male sex, and is responsible for 350,000 deaths every year [15]. Although debate continues as to the benefit of prostate cancer screening on all-cause mortality [16], prostate-specific antigen (PSA) testing has now been endorsed by the vast majority of international guidelines as an inexpensive, low-invasive, and relatively accurate means of detection for purpose of prostate cancer screening [17]. Moreover, it has been recently found that routine PSA testing would improve the detection of any type of prostate cancer, especially the localized forms. As such, it has been emphasized that a decrease in PSA screening would cause a substantial reduction in prostate cancer detection, with non-negligible increase in prostate cancer-specific mortality [18].

Therefore, the aim of this study was to analyze the volume of PSA test requests placed to a local service of laboratory medicine, compared to those of vitamin D (Vit D; i.e., the most requested immunochemical test in local laboratories), to establish if and how the ongoing COVID-19 outbreak may have impacted the local practice of routine prostate cancer screening in the province of Verona, Italy.

MATERIALS AND METHODS

The Service of Laboratory Medicine of the University Hospitals of Verona encompasses two separate medical laboratories, one in the Policlinic (~600-bed facility) and the other in the General Hospital (~1200-bed facility), located at the opposite sides of the town of Verona (Southbound and Northbound, respectively). These two hospitals serve an area of 3096 km², with a population of nearly 922,000 inhabitants, and provide both routine and urgent testing, averaging a total of ~6 million tests in 2019 (60.8% of which in the Policlinic, 46.0% for outpatients). Routine and urgent laboratory testing for inpatients and outpatients was preserved throughout the COVID-19-related lockdown period within the Verona province (i.e., between March 10 and May 17, 2020), as access to routine laboratory testing was exempted from national, regional, and provincial restrictions.

An electronic search was carried out in the local laboratory information system (LIS; Concerto, Dedalus Italia, Firenze, Italy) database to identify all test requests placed in both laboratories for total PSA and Vit D in outpatients during the last five years (i.e., from December 10, 2016, to December 10, 2020). The number of new daily diagnoses of SARS-CoV-2 infection in Italy and Verona's province was retrieved from the official website of the Italian National Institute of Health (Istituto Superiore di Sanità; ISS). Both PSA (assayed with Roche Elecsys, Roche

Diagnostics, Rotkreuz, Switzerland) and Vit D (measured with Liaison XL, DiaSorin, Saluggia, Italy) tests were freely available for request, and the local guidelines regulating their prescription remained unchanged throughout the study period, as well as the analytical platforms. The weekly volume of total PSA and Vit D outpatient tests during the different periods was reported as median with interquartile range (IQR). The significance of differences and correlations were assessed with Mann-Whitney U and Spearman's tests, respectively. The variation in the number of weekly test requests placed to the local laboratories for both Vit D and total PSA in 2020 compared to the same weeks of the previous four years was expressed as a ratio (i.e., [weekly test requests in 2020] / [mean weekly test requests between 2016-2019]). Statistical analysis was performed using Analyse-it (Analyse-it Software Ltd, Leeds, UK) and MedCalc (MedCalc Software Ltd, Ostend, Belgium). The study was conducted in accordance with the Declaration of Helsinki, under the terms of relevant local legislation. The entire work was based on anonymized searches in the local LIS as part of a systematic laboratory workflow analysis. Therefore, no informed consent or ethics committee approval was necessary.

RESULTS

The cumulative number of weekly diagnoses of SARS-CoV-2 infections in Italy and the Verona province since the beginning of the local outbreak (i.e., February 25, 2020) is shown in Figure 1. Two distinct "waves" can be seen, interspersed by the summer months of the year. A significant correlation was found between the number of weekly COVID-19 diagnoses in Italy and those specifically recorded in the Verona province ($r=0.95$; 95% CI, 0.93-0.96; $p<0.001$).

The cumulative number of weekly test requests for Vit D and total PSA, as recorded between

February 25 and December 10, 2020, is summarized in Table 1. Although the volume of test requests placed for both Vit D and total PSA throughout this period did not differ in 2020 compared to the mean number recorded during the same period of the previous four years, a dramatic decline could be observed during the lockdown period in the province of Verona, with median decrease of 76% (IQR, -84% to -40%) for Vit D and 62% (IQR, -79% to -41%) for total PSA respectively. An opposite trend could be observed

when test requests for both Vit D and total PSA were analyzed during periods of 2020 without lockdown restrictions as compared to the mean number recorded during the same weeks of the previous four years. More specifically, the test requests exhibited a median increase of 13% (IQR, 5% to 29%) for Vit D and 43% (IQR, 24% to 54%) for total PSA. These same trends can also be seen in the variation ratio between test requests placed in 2020 and the previous four years (Figure 2).

Figure 1 Cumulative number of weekly diagnoses of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in Italy and Verona's province since the beginning of the local outbreak (i.e., since February 25, 2020)

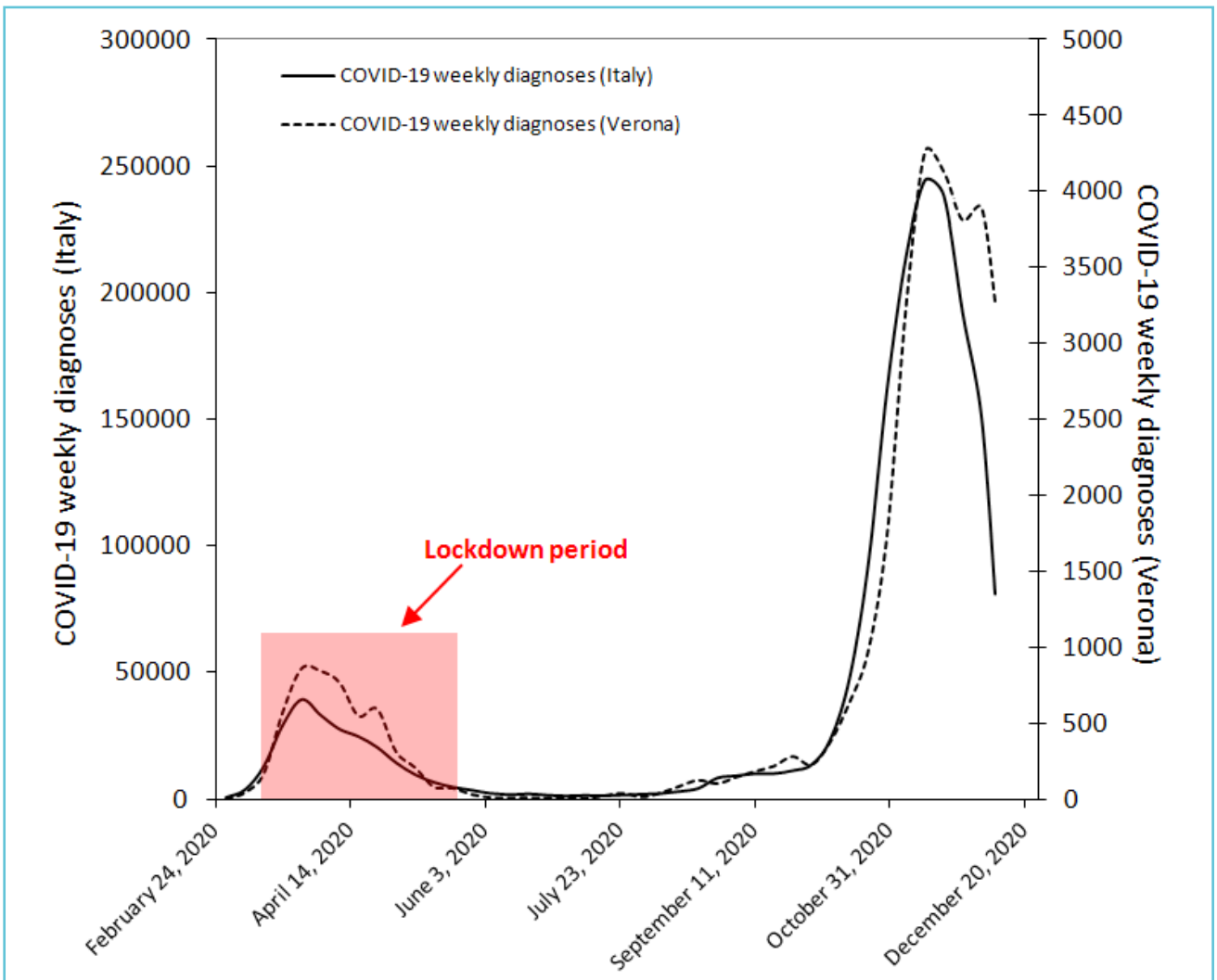


Table 1 Weekly number of Vitamin D (Vit D) and total prostate-specific antigen (PSA) requests placed to the local laboratories between February 25 and December 9, 2020, compared to the mean number of requests placed during the same week of the previous four years (i.e., 2016-2019)

Analyte	Test requests in 2020	Mean test requests in 2016-2019	p
Vit D			
Total period	278 (196-319)	268 (232-285)	0.192
Lockdown period*	66 (48-126)	283 (271-288)	<0.001
No lockdown period	295 (267-322)	256 (228-280)	<0.001
Total PSA			
Total period	171 (126-196)	138 (117-151)	0.052
Lockdown period*	52 (29-76)	146 (129-147)	<0.001
No lockdown period	181 (165-201)	135 (116-151)	<0.001

Results are shown as median with interquartile range (IQR).

* Lockdown period was between March 10 and May 17, 2020.

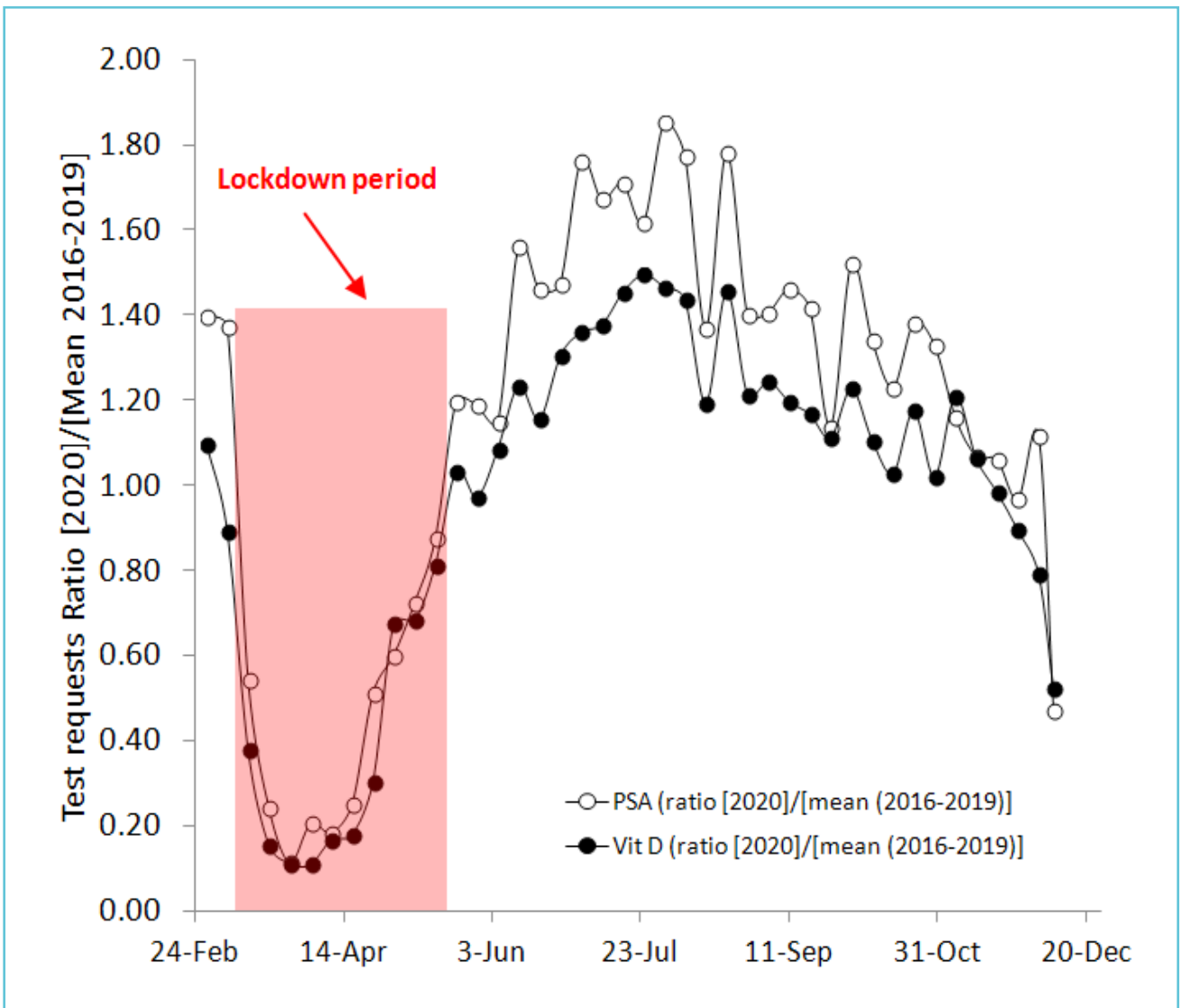
A significant correlation was found between the variation in test requests placed from February 25, 2020, to December 10, 2020, compared to the same period of the previous four years, for Vit D versus total PSA, ($r = 0.94$; 95% CI, 0.90-0.97; $p < 0.001$).

DISCUSSION

The results of our analysis of Vit D and total PSA test requests placed for outpatients in a Northern Italian town since the beginning of the COVID-19 outbreak shows that the lockdown resulted in a dramatic decrease in the number of total PSA and Vit D tests performed, despite the fact that local restrictions did not include a ban on access to routine diagnostic testing.

The reduction in test requests for both assays, as high as 76% for Vit D and 62% for total PSA, were likely due to identical causes (i.e., fear of being infected by leaving home, derangement of public transportation, lacking or inefficient communication that routine laboratory testing was still allowed and available), as a virtually perfect correlation could be found between the number of missing Vit D and total PSA analyses. These findings are congruent with those reported by De Vincentiis et al. [19], who reported that the number of histological prostate cancer diagnoses was decreased by 75% in 2020 compared to the average number recorded in the previous two years at a secondary care hospital network in central Italy. It can thus be proffered that the establishment of a generalized lockdown,

Figure 2 Variation in the number of weekly test requests for Vitamin D (Vit D) and total prostate-specific antigen (PSA) between February 25 and December 9 in 2020 compared to the mean number of weekly requests placed in the previous four years (i.e., 2016-2019). The values are expressed as a ratio, calculated as: [weekly test requests in 2020] / [mean weekly test requests between 2016-2019]



without restrictions on access to routine care, may still have dramatic consequences on cancer screening policies, with PSA representing a paradigmatic example. While the increased volume of testing recorded in the post-lockdown period may have filled the gap observed during the lockdown period in terms of total number of

annual tests (Figure 2 and Table 1), this will not void the delay that may have occurred in diagnosing some prostate cancers, whose prognosis is negatively influenced by inaccurate or delayed detection [20].

Although the putative benefits may vary largely among the different types of malignant diseases,

there is now clear, unquestionable evidence that a timely diagnosis may improve cancer survival and enhance patient quality of life. In a systematic review, Neal et al. concluded that a delayed diagnosis might negatively impact the outcomes of colorectal, breast, testicular, head and neck, pancreatic, bladder, and prostate cancers [21]. With respect specifically to prostate cancer, O'Brien reported that surgical delay may be associated with poorer prostatectomy outcomes, including a significantly adverse progression of disease, even in patients with low-risk prostate cancer criteria [22]. In a more recent study, Banerji et al. revealed that a reduction in the number of PSA tests was associated with increased likelihood of diagnosing higher clinical stage disease, potentially leading to many avoidable cancer deaths [23]. Almost identical findings were reported by Qu et al., who showed that diagnostic delay of 1 month or longer was associated with higher clinical stage and biopsy grade [24]. In keeping with these findings, Tørring and colleagues elucidated the existence of a significant association between a longer diagnostic interval and enhanced prostate cancer mortality [25]. On the contrary, a recent study failed to show negative survival outcomes when radical prostatectomy was delayed up to 6 months in patients with clinically localized, high-risk prostate adenocarcinoma [26]. However, Sun and colleagues highlighted that a treatment delay of around three months between diagnosis and prostatectomy may require more extensive periprostatic tissue ablation, thus impairing erectile function and postoperative continence [27]. Last but not least, missing or delaying active surveillance, with PSA testing considered a central part of prostate cancer follow-up, may also have dramatic consequences on disease progression or relapse, as supported by a recent meta-analysis by Enikeev et al. [28]. In conclusion, the lockdown period imposed during the first wave of the COVID-19 outbreak in the Verona province of Italy was associated

with a dramatic decrease in total PSA test requests (and Vit D) requisition from the local laboratories. Since evidence exists that shorter time to diagnosis is associated with more favorable outcome for prostate cancer, as well as for many other malignancies, the restrictive measures applied for containing SARS-CoV-2 spread in the community should be accompanied by improved communication and clear warnings by both public health authorities and medical care givers that essential cancer screenings should not be abandoned or delayed. Notably, extensive resource re-allocation is constantly demanded during this ongoing COVID-19 pandemic outbreak. Rationalization in healthcare utilization is of paramount importance, and may become a definite reason for unavoidable collateral consequences. COVID-19 may also have dramatic implications on routine laboratory testing, and our observed decrease in Vit D test requests may not only reflect underutilization, but perhaps also a more rationalized use of routine laboratory services.

REFERENCES

1. Lippi G, Sanchis-Gomar F, Henry BM. COVID-19: unravelling the clinical progression of nature's virtually perfect biological weapon. *Ann Transl Med* 2020;8:693.
2. Lippi G, Henry BM, Bovo C, Sanchis-Gomar F. Health risks and potential remedies during prolonged lockdowns for coronavirus disease 2019 (COVID-19). *Diagnosis (Berl)* 2020;7:85-90.
3. Sabatello M, Burke TB, McDonald KE, Appelbaum PS. Disability, Ethics, and Health Care in the COVID-19 Pandemic. *Am J Public Health* 2020;110:1523-1527.
4. De Rosa S, Spaccarotella C, Basso C, Calabrò MP, Curcio A, Filardi PP, Mancone M, Mercuro G, Muscoli S, Nodari S, Pedrinelli R, Sinagra G, Indolfi C; Società Italiana di Cardiologia and the CCU Academy investigators group. Reduction of hospitalizations for myocardial infarction in Italy in the COVID-19 era. *Eur Heart J* 2020;41:2083-8.
5. Mafham MM, Spata E, Goldacre R, Gair D, Curnow P, Bray M, Hollings S, Roebuck C, Gale CP, Mamas MA, Deanfield JE, de Belder MA, Luescher TF, Denwood T, Landray MJ, Emberson JR, Collins R, Morris EJA, Casadei B, Baigent C. COVID-19 pandemic and admission rates for

and management of acute coronary syndromes in England. *Lancet* 2020;396:381-389.

6. Tam CF, Cheung KS, Lam S, Wong A, Yung A, Sze M, Lam YM, Chan C, Tsang TC, Tsui M, Tse HF, Siu CW. Impact of Coronavirus Disease 2019 (COVID-19) Outbreak on ST-Segment-Elevation Myocardial Infarction Care in Hong Kong, China. *Circ Cardiovasc Qual Outcomes* 2020;13:e006631.

7. Nef HM, Elsässer A, Möllmann H, Abdel-Hadi M, Bauer T, Brück M, Eggebrecht H, Ehrlich JR, Ferrari MW, Fichtlscherer S, Hink U, Hölschermann H, Kacapor R, Koeth O, Korboukov S, Lamparter S, Laspoulas AJ, Lehmann R, Liebetau C, Plücker T, Pons-Kühnemann J, Schächinger V, Schieffer B, Schott P, Schulze M, Teupe C, Vasa-Nicotera M, Weber M, Weinbrenner C, Werner G, Hamm CW, Dörr O; CoVCAAD –Study Group. Impact of the COVID-19 pandemic on cardiovascular mortality and catheterization activity during the lockdown in central Germany: an observational study. *Clin Res Cardiol*. 2020 Nov 21:1–10. doi: 10.1007/s00392-020-01780-0. Epub ahead of print

8. Fu SJ, George EL, Maggio PM, Hawn M, Nazerali R. The Consequences of Delaying Elective Surgery: Surgical Perspective. *Ann Surg*. 2020 Apr 29. doi: 10.1097/SLA.0000000000003998.

9. Reichert M, Sartelli M, Weigand MA, Doppstadt C, Hecker M, Reinisch-Liese A, Bender F, Askevold I, Padberg W, Coccolini F, Catena F, Hecker A; WSES COVID-19 emergency surgery survey collaboration group. Impact of the SARS-CoV-2 pandemic on emergency surgery services—a multi-national survey among WSES members. *World J Emerg Surg* 2020;15:64.

10. Atia F, Pocnetz S, Selby A, Russell P, Bainbridge C, Johnson N. The effect of the COVID-19 lockdown on hand trauma surgery utilization. *Bone Jt Open* 2020;1:639-643.

11. Peric S, Stulnig TM. Diabetes and COVID-19: Disease-Management-People. *Wien Klin Wochenschr*. 2020 Jul; 132(13-14):356-361. doi: 10.1007/s00508-020-01672-3. Epub 2020 May 20. PMID: 32435867.

12. Maringe C, Spicer J, Morris M, Purushotham A, Nolte E, Sullivan R, Rachet B, Aggarwal A. The impact of the COVID-19 pandemic on cancer deaths due to delays in diagnosis in England, UK: a national, population-based, modelling study. *Lancet Oncol* 2020;21:1023-34.

13. Czeisler MÉ, Marynak K, Clarke KEN, Salah Z, Shakya I, Thierry JM, Ali N, McMillan H, Wiley JF, Weaver MD, Czeisler CA, Rajaratnam SMW, Howard ME. Delay or Avoidance of Medical Care Because of COVID-19-Related Concerns - United States, June 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:1250-7.

14. Lazzarini M, Barbi E, Apicella A, Marchetti F, Cardinale F, Trobia G. Delayed access or provision of care in Italy

resulting from fear of COVID-19. *Lancet Child Adolesc Health* 2020;4:e10-e11.

15. Mattiuzzi C, Lippi G. Current Cancer Epidemiology. *J Epidemiol Glob Health* 2019;9:217-222.

16. Lippi G, Montagnana M, Guidi GC, Plebani M. Prostate-specific antigen-based screening for prostate cancer in the third millennium: useful or hype? *Ann Med* 2009;41:480-9.

17. Tikkinen KAO, Dahm P, Lytvyn L, Heen AF, Vernooij RWM, Siemieniuk RAC, Wheeler R, Vaughan B, Fobuzi AC, Blanker MH, Junod N, Sommer J, Stirnemann J, Yoshimura M, Auer R, MacDonald H, Guyatt G, Vandvik PO, Agoritsas T. Prostate cancer screening with prostate-specific antigen (PSA) test: a clinical practice guideline. *BMJ* 2018; 362:k3581.

18. Ilic D, Djulbegovic M, Jung JH, Hwang EC, Zhou Q, Cleves A, Agoritsas T, Dahm P. Prostate cancer screening with prostate-specific antigen (PSA) test: a systematic review and meta-analysis. *BMJ* 2018;362:k3519.

19. De Vincentiis L, Carr RA, Mariani MP, Ferrara G. Cancer diagnostic rates during the 2020 'lockdown', due to COVID-19 pandemic, compared with the 2018-2019: an audit study from cellular pathology. *J Clin Pathol*. 2020 Jun 19:jclinpath-2020-206833. doi: 10.1136/jclinpath-2020-206833. Epub ahead of print.

20. Lazzeri G, Troiano G, Porchia BR, Centauri F, Mezzatesta V, Presicce G, Matarrese D, Gusinu R. Waiting times for prostate cancer: A review. *J Public Health Res* 2020;9:1778.

21. Neal RD, Tharmanathan P, France B, Din NU, Cotton S, Fallon-Ferguson J, Hamilton W, Hendry A, Hendry M, Lewis R, Macleod U, Mitchell ED, Pickett M, Rai T, Shaw K, Stuart N, Tørring ML, Wilkinson C, Williams B, Williams N, Emery J. Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review. *Br J Cancer* 2015;112 Suppl 1:S92-107.

22. O'Brien D, Loeb S, Carvalhal GF, McGuire BB, Kan D, Hofer MD, Casey JT, Helfand BT, Catalona WJ. Delay of surgery in men with low risk prostate cancer. *J Urol* 2011;185:2143-70.

23. Banerji JS, Wolff EM, Massman JD 3rd, Odem-Davis K, Porter CR, Corman JM. Prostate Needle Biopsy Outcomes in the Era of the U.S. Preventive Services Task Force Recommendation against Prostate Specific Antigen Based Screening. *J Urol* 2016;195:66-73.

24. Qu LG, Nzenza T, McMillan K, Sengupta S. Delays in prostate cancer care within a hospital network in Victoria, Australia. *ANZ J Surg* 2019;89:1599-1604.

25. Tørring ML, Frydenberg M, Hansen RP, Olesen F, Vedsted P. Evidence of increasing mortality with longer

diagnostic intervals for five common cancers: a cohort study in primary care. *Eur J Cancer* 2013;49:2187-98.

26. Xia L, Talwar R, Chelluri RR, Guzzo TJ, Lee DJ. Surgical Delay and Pathological Outcomes for Clinically Localized High-Risk Prostate Cancer. *JAMA Netw Open* 2020;3:e2028320.

27. Sun M, Abdollah F, Hansen J, Trinh QD, Bianchi M, Tian Z, Briganti A, Shariat SF, Montorsi F, Perrotte P, Karakiewicz PI. Is a treatment delay in radical prostatectomy safe in

individuals with low-risk prostate cancer? *J Sex Med* 2012;9:2961-9.

28. Enikeev D, Morozov A, Taratkin M, Barret E, Kozlov V, Singla N, Rivas JG, Podoinitsin A, Margulis V, Glybochko P. Active Surveillance for Intermediate-Risk Prostate Cancer: Systematic Review and Meta-analysis of Current Protocols and Outcomes. *Clin Genitourin Cancer*. 2020 May 22:S1558-7673(20)30116-6. doi: 10.1016/j.clgc.2020.05.008. Epub ahead of print.