

4K[®] score test in the time of COVID-19 quarantine - implications for timely diagnosis of high-risk prostate cancer

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Abstract

The diagnosis of clinically significant prostate cancer is often challenging. The 4K[®] score test may assist in evaluating the risk of significant malignancy and avoid biopsies in non-significant disease. The COVID-19 pandemic caused a remarkable disruption in managing patients with suspected prostate cancer. The aim of this study is to evaluate the effect of the COVID-19 pandemic on 4K[®] score test results by comparing tests performed in Israel between April to July 2020 to a control group of the same period in 2019. During the COVID-19 era there were few quarantine periods in which citizens were allowed to leave their homes for specific reasons only (eg, medical consultations). Meanwhile, medical clinics were operating in limited schedule with intention to treat emergent cases only. We assumed that focusing on coping with the pandemic and its implications will decrease prostate MRI tests and prostate biopsies and as a result, there will be an increase in the 4K score blood tests as well as a change in the pre-biopsies prostate risk stratification.

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Conflict of interests

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Abstract

Background

The diagnosis of clinically significant prostate cancer is often challenging. The 4K[®] score test may assist in evaluating the risk of significant malignancy and avoid biopsies in non-significant disease. The COVID-19 pandemic caused a remarkable disruption in managing patients with suspected prostate cancer.

The aim of this study is to evaluate the effect of the COVID-19 pandemic on 4K[®] score test results by comparing tests performed in Israel between April and July 2020 to a control group of the same period in 2019.

We assumed that focusing on coping with the pandemic and its implications will decrease prostate MRI tests and prostate biopsies and as a result, there will be an increase in the 4K score blood tests as well as a change in the pre-biopsies prostate risk stratification.

Methods - A retrospective cohort study comparing the characteristics of the study group to the control group was done using diagnostic multi-variables statistical analysis.

Results - A 37% reduction in the number of 4K[®] score tests performed (450 versus 721) was noted. The reduction was seen mainly among men older than 65 years. A significantly higher percentage of patients with 4K[®] scores indicating a high risk of clinically significant prostate cancers (>20%) was noted among men younger than 65 years compared to the control group.

Conclusions - The COVID-19 pandemic had an influence on the number of tests performed, especially in the elderly. Delay or lack of supportive imaging during the pandemic may be the reason for the higher 4K[®] scores among younger patients.

The reduction in the number of 4K tests on the one hand and the fact that non-urgent diagnostic procedures and exams (eg prostate MRI exams, prostate biopsies etc.) were less available during the COVID-19 era could have caused a delay in prostate cancer diagnosis and treatment.

Key words - 4K[®] score test, COVID-19, prostate cancer, PSA.

Introduction

Prostate cancer is the most common malignancy among men [1]. For many years the evaluation and diagnosis of this disease was based on PSA blood test [2] and digital rectal examination (DRE). In the last decade, new tests are available and may assist physicians distinguish between patients who harbor a high-risk significant prostate cancer and those with low-risk prostate cancer and thus rationally select patients who need prostate biopsies. One of the diagnostic options today is the 4K[®] score test which is a blood test sampling the level of three serological markers besides the PSA: free PSA, intact PSA and human kallikrein-related peptidase 2 (hK2) [3]. Different studies reported a greater efficiency in diagnosing aggressive prostate cancer by using the 4K[®] score test comparing the standard PSA level, allowing avoiding biopsies among patients assuming to have less aggressive disease [4,5].

Patients with 4K[®] score of 7.5% or less are considered to have a low-risk for diagnosis of a prostate cancer of Gleason score of 7 or higher if a biopsy was performed. Also, these patients have less than a 1% risk of having metastasis within 20 years [6]. In contrast, patients with a 4K[®] score above 33% are 33% more likely to have a Gleason score [?]7 prostate cancer if a biopsy was performed [4, 7].

COVID-19 has a global effect with substantial mortality as well as indirect effect on evaluating other diseases [8], reducing human resources, reducing budgets, directing clinics to treat only COVID-19 patients, and reducing primary evaluating facilities with local or regional instructions to reduce visits in hospitals and outpatient clinics with other diseases. This reality may cause delayed diagnosis of other diseases, including

malignancies. The diagnosis rates of different malignancies reduced significantly in USA comparing the pre-COVID 19 era, a finding which its implications may be noticeable for years to come [9]. A study using a mathematical model to evaluate the expected influence of a delayed diagnosis on the mortality rate, predicted an incline in preventable mortality rate the next years among patients with different malignancies [10].

In Israel, during the COVID era, few quarantine periods were declared in which people were instructed not to leave their homes unless for prespecified reasons such as essential medical treatment. In addition to that, the Israeli ministry of health instructed hospitals and clinics to reduce elective procedures.

Goal

The goal of this study is to evaluate the effect of the COVID-19 pandemic on the 4K (r) score test array among men in Israel.

Methods

This is a retrospective cohort study evaluating the results of 4K (r) score tests performed in Israel before and during the COVID-19 pandemic.

Institutional ethical approval was obtained. The Data was obtained and collected anonymously from the Bioreference Laboratories which performs the 4K scores in Israel; As this is the only one lab in Israel responsible for 4K tests, the numbers and results represent the entire tests performed in Israel in a given period. As the data is retrospective and anonymous some details are missing such as family history of prostate cancer, findings on digital rectal examination, previous TURS-guided biopsies and the results and PSA kinetics

The study group was defined as males who completed the 4K (r) score tests between April 1st 2020 and July 31st 2020 during the first quarantine period in Israel. The control group was defined as males who completed the tests during April-July 2019, before the COVID-19 pandemic. Clinical and demographic data were compared between the groups. Multivariate analyses were used to define factors independently associated with 4K(r) scores indicating increased risk for malignancy.

The primary outcome was defined as the percentage of patients with a 4K (r) score above 20% indicating an increased risk for a clinically significant prostate cancer [4]. Secondary outcomes were the percentages of patients with 4K (r) scores indicating a low-risk and a very high-risk for clinically significant prostate cancers (<7.5% and >33%, respectively).

The database was obtained from Bioreference Laboratories, which performs the tests in Israel. The bilateral value of 0.05 was defined as statistically significant. All statistical analyses were performed using IPSS software version 25.

The study was approved by local Helsinki committee. As the study is retrospective and does not identify patients, a waiver of informed consent was granted by the ethical committee.

Results:

The study included 1171 subjects. The study group included 450 patients for whom 4K (r) tests were performed during April-July 2020 whereas the control group included 721 patients for whom tests were performed during April-July 2019. The age range was between 41 and 86 years and the mean age was similar between the two groups (66 versus 67 years in the study and control groups, respectively, $p=0.535$). The mean PSA level was similar between the two groups (7, $p=0.865$) – Table 1.

Table 2 shows 4K (r) scores divided using 7.5%, 20% and 33% cut-offs, dividing patients to low-risk ([?]7.5%), moderate-risk (7.5%<4K (r) score [?]20%), high-risk (>20%) and very high-risk (>33%). As could be seen, a higher percentage of patients in the study group had a 4K (r) score >20% indicating a high risk for clinically significant prostate cancer [146/450 (32.4%) versus 195/721 (27%), respectively, $p=0.048$]. Similarly, a very high risk of malignancy with 4K (r) of 33% or more, was found to be significantly more common in the study group [80/450 (18%) versus 93/721 (13%), $p=0.022$]. On the other hand, there was no significant difference

between the study group and the control group regarding low-risk range [164/450 (36.4%) versus 279/721 (39%) respectively, $P>0.1$].

When examining the results distributed by age groups – 65 years or younger and older than 65 (table 3), we can see that there was a significant difference between the study group and the control group in patients 65 years old and younger using 4K (r) scores of 20% [68 (32.2%) versus 43 (16.6%), respectively, $p<0.05$] and 33% [35 (16.6%) versus 13 (5%), respectively, $p<0.05$]. on the other hand, there was no significant difference between the groups in patients older than 65 using 4K (r) scores of 20% and 33% [45 (18.8%) versus 80 (17.3%), respectively, $p=0.62$].

Discussion:

Prostate cancer is the most common cancer in men [11]. Since the beginning of screening for prostate cancer with serum PSA, we have seen a significant decline in prostate cancer mortality [12].

A systematic analysis suggested that up to 60% of prostate cancers diagnosed in contemporary studies can be safely observed without a need for immediate intervention [13]. However, 20% to 30% of men who are diagnosed with prostate cancer are found to have high-grade disease at presentation [14]. Diagnosis should focus on detection of aggressive tumors, that are more likely to progress to metastatic disease and death, and not the indolent ones.

The 4K (r) scores test is a relatively new blood test that identifies the risk of aggressive cancer and has a role as an initial test before performing prostate biopsies in men with an elevated PSA level or an abnormal digital rectal examination result, or after a previous negative prostate biopsy with persistently elevated PSA level. The test result is a personalized positive predictive value of finding Gleason score ≥ 7 cancer on biopsy of the prostate. This provides the patient and physician with quantitative information to aid in clinical decision making regarding performing prostate biopsies.

The COVID-19 era in general had a major effect on health-care related issues such as allocating medical resources to cope with COVID and its implications, delaying or postponing non-emergent diagnostic procedures and even limited availability of primary care providers, not to mention expert consultation

This study is intended to examine the extent of the effect during the first quarantine period of COVID-19 pandemic on performing 4K(r) blood tests in Israel. We found that the number of tests performed during the study period decreased significantly by about 37% compared to the corresponding period the year before. This fact is consistent with that described in the literature on reduction in malignancy-related tests during the COVID-19 period. One of the subjects being investigated recently is the risk of late diagnosis and mortality from life-threatening diseases in general [15] and cancer in particular [16]. These studies found an increased risk of morbidity and mortality from serious diseases due to neglect and reduction in follow-up and late diagnosis of malignant diseases during this period.

Another component is the psychological consequences of living during a pandemic that causes anxiety and seclusion that have a negative effect on the diagnosis and treatment of patients with serious illnesses [17].

Our study found a significant difference between the study and control groups in the percentage of tests indicating a high-risk (4K(r) score above 20%) and a very high-risk (4K (r) score above 33%) for clinically significant prostate cancer.

A reasonable explanation for these differences would have been an increased PSA levels during screening, which incited both the referring physician and the patient to perform the 4K(r) test. However, no significant difference in PSA level was found between the study group and the control group. The mean age was not significantly different between the groups but the ratio of patients 65 years or younger out of the total subjects in the study period ($211/450=0.47$) was higher relative to their ratio in the control group ($259/721=0.36$). This may be because older patients tended to be more isolated and secluded during the first quarantine period included in the study period.

The patients' age was found to be an influencing factor on higher 4K (r) scores during the study period, even in multivariable analysis. During the study period, more patients aged 65 or younger with high 4K(r) scores were found compared to the corresponding period the year before. One possible explanation is that 4K (r) tests were performed instead of MRI imaging that were canceled or postponed due to the pandemic working schedule [18].

This is the first study to address the implications of this challenging era on the diagnosis of prostate cancer using biological markers.

The strengths of the study are a uniform database with a large number of tests performed in one central laboratory.

The limitations of the study are a relatively short period of time during the pandemic period taken as the study period as well as the lack of the actual biopsy results.

Extensive research with a larger database is required to validate the research findings.

Conclusions and summary:

The number of tests performed among patients older than 65 years has decreased during the study period, possibly because of the quarantine and the concerns related to performing blood tests during this period. On the other hand, there was an increase in the percentage of the tests indicating a high-risk disease among men aged 65 years or younger, possibly because of less accessibility to other imaging tests during the pandemic period following the outbreak of COVID-19.

Table 1 – baseline characteristics of men in the study

Characteristics	Study group	Control group	P-value
Number of patients	450	721	-
Mean age (yr)	66	67	P=0.535
Mean PSA [ng/ml]	7.08	7.03	P=0.865

Table 2 – 4K (R) scores divided using 7.5%, 20% and 33% cut-offs , dividing patients to low-risk ([?]7.5%) ,moderate-risk (7.5%<4K (r) score [?]20%), high-risk (>20%) and very high-risk (>33%)

4K (R) score	Time frame	Time frame	Total	P-value
	April-July 2019 – Control group	April-July 2020 – study group		?
7.5% - low-risk	279 (39%)	164 (36.4%)	443 (37.8%)	P>0.1
>7.5% -moderate-risk	442 (61%)	286 (63.6%)	728 (62.2%)	?
20% - moderate-risk	526 (73%)	304 (67.6%)	830 (70.9%)	P<0.05
>20% - high-risk	195 (27%)	146 (32.4%)	341 (29.1%)	?
33%	628 (87.1%)	370 (82.2%)	998 (85.2%)	P<0.05
>33%	93 (12.9%)	80 (17.8%)	173 (14.8%)	

Table 3 – 4K (R) scores distribution by age groups

Age group	4K (R) score	Time frame	Time frame	Total
		April-July 2019 – Control group	April-July 2020 – study group	
65	[?] 20%	216 (83.4%)	143 (67.8%)	359 (76.4%)
	>20%	43 (16.6%)	68 (32.2%)	111 (23.6%)

Age group	4K $\text{\textcircled{R}}$ score	Time frame	Time frame	Total
>65	[?]33%	246 (95%)	176 (83.4%)	422 (89.8%)
	>33%	13 (5%)	35 (16.6%)	48 (10.2%)
	[?] 20%	310 (67.1%)	161 (67.4%)	471 (67.2%)
	>20%	152 (32.9%)	78 (32.6%)	230 (32.8%)
	[?]33%	382 (82.7%)	194 (81.2%)	576 (82.2%)
	>33%	80 (17.3%)	45 (18.8%)	125 (17.8%)

Data availability :

The data that support the findings of this study are available from the corresponding author (M.Y) upon reasonable request.

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