European Journal of Surgical Oncology 47 (2021) 2640–2645

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Rotterdam mobile phone app including MRI data for the prediction of prostate cancer: A multicenter external validation

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ARTICLE INFO

Article history:
Received 8 March 2021
Received in revised form
19 April 2021
Accepted 26 April 2021
Available online 30 April 2021

Keywords:
Prostate cancer
Medical app
Magnetic resonance
Nomogram

ABSTRACT

Objectives: The Rotterdam Prostate Cancer Risk calculator (RPCRC) has been validated in the past years. Recently a new version including multiparametric magnetic resonance imaging (mpMRI) data has been released. The aim of our study was to analyze the performance of the mpMRI RPCRC app.

Methods: A series of men undergoing prostate biopsies were enrolled in eleven Italian centers. Indications for prostate biopsy included: abnormal Prostate specific antigen levels (PSA>4 ng/ml), abnormal DRE and abnormal mpMRI. Patients' characteristics were recorded. Prostate cancer (PCa) risk and high-grade PCa risk were assessed using the RPCRC app. The performance of the mpMRI RPCRC in the prediction of cancer and high-grade PCa was evaluated using receiver operator characteristics, calibration plots and decision curve analysis.

Results: Overall, 580 patients were enrolled: 404/580 (70%) presented PCa and out of them 224/404 (55%) presented high-grade PCa. In the prediction of cancer, the RC presented good discrimination (AUC = 0.74), poor calibration (p = 0.01) and a clinical net benefit in the range of probabilities between 50 and 90% for the prediction of PCa (Fig. 1). In the prediction of high-grade PCa, the RC presented good discrimination (AUC = 0.79), good calibration (p = 0.48) and a clinical net benefit in the range of probabilities between 20 and 80% (Fig. 1).

Conclusions: The Rotterdam prostate cancer risk App accurately predicts the risk of PCa and particularly high-grade cancer. The clinical net benefit is wide for high-grade cancer and therefore its implementation in clinical practice should be encouraged. Further studies should assess its definitive role in clinical practice.

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https://doi.org/10.1016/j.ejso.2021.04.033
0748-7983/

Introduction

Prostate cancer (PCa) is the most common malignancy diagnosed in men [1]. PCa diagnosis depends on prostate biopsies, often based on Prostatic Specific Antigen (PSA) levels and/or abnormal Digital Rectal Examination (DRE) [2]. However, PSA and DRE present a low accuracy for the detection of PCa and a high number of unnecessary prostate biopsies are normally prescribed. Since 2019, the European Association of Urology (EAU) guidelines recommends an individualized risk assessment of the patient using risk calculators, multi-parametric magnetic resonance imaging (mpMRI) and eventually an additional serum or urine marker [3]. Notwithstanding the development of these new diagnostic tools, a large number of unnecessary prostate biopsies are still performed, and clinically insignificant cancers are diagnosed.

In the past years, many authors have developed PCa risk calculators in different populations to enhance the diagnostic accuracy of PSA [4–6]. However, most of these calculators are now outdated considering that they do not include mpMRI data in their models which is now indicated by the EAU guidelines before the first set of prostate biopsies in men at increased risk of PCa [7–9]. One of the most known calculators for the risk assessment of PCa is the Rotterdam Prostate Cancer Risk Calculator (RPCRC), based on the ERSPC Rotterdam data [10], which is now available as a mobile phone App too. However the few studies that have validated the new RPCRC present some methodological limitations and lack data on high-risk patients [8,11]. With this knowledge in mind, the aim of our study was to analyze the performance of the mpMRI RPCRC app in a multicenter cohort of Italian patients undergoing prostate biopsies.

Material and methods

A consecutive series of men undergoing fusion prostate biopsies were enrolled in eleven Italian centers. All patients signed a dedicated informed consent, and the study was conducted in accordance with the principles of the declaration of Helsinki.

Indications for prostate biopsies included: PSA>4 ng/ml and/or abnormal DRE and/or abnormal mpMRI (PIRADS score >2). All patients with a PSA>4 ng/ml and/or abnormal DRE underwent a mpMRI and the biopsy was performed even in those cases with a negative mpMRI. Patients with a previous diagnosis of PCa, PSA <0.4 ng/mL or >30 ng/mL, or prostate volume (PV) <10 mL or >110 mL were excluded. DRE was performed by a senior staff urologist and judged positive if suggestive of cancer. Prostatic Volume, age and anthropometric parameters including Body Mass Index (BMI) were recorded from all patients. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m2).

mpMRI was performed in each center using a 1,5 T MRI. mpMRI were graded according to PIRADS score v2 by a dedicated radiologist in each center. No central review of mpMRI data was performed [12].

Every patient underwent a fusion prostatic biopsy, *trans*-rectal or *trans*-perineal, according to the mpMRI results. All the biopsies were performed by experienced urologist (>100 procedures per year). Patients underwent 12 random biopsies and 3 biopsies per lesion [13] [–] [17]. Patients with a negative mpMRI underwent only random biopsies [15]. All biopsies were pathologically reviewed in the institute of origin by a single dedicated pathologist in each center. Low-grade disease was defined as Gleason 6 and high-grade disease as Gleason ≥7 as defined by the mobile apps [11]. Total PSA was measured the day of the biopsy [14,18].

PCa risk and high-grade PCa risk were assessed using the Rotterdam Prostate Cancer Risk Calculator app called Prostate Cancer Risk (iOS: https://itunes.apple.com/app/rotterdam-prostate-cancer/id729313737?mt=8; Android: https://play.google.com/store/apps/details?id=com.rpcrc). The RPCRC app includes data on mpMRI data (PIRADS score), age, previous negative biopsies, DRE outcome, PSA, and PV (evaluated with DRE or TRUS and expressed in ml). In the validation process the app results were adjusted for the prevalence of cancer and high-grade cancer of our cohort [19].

Statistical analysis

Statistical analysis was performed using SPSS 24 (IBM, statistical software) and STATA software (Stata software version 14, StataCorp 2015 Stata Statistical Software: Release 14, College Station, TX: StataCorp LP). Continuous variables are presented as median and interquartile ranges (IQRs) and were compared by the Student independent *t*-test, the Mann Whitney *U* test or Kruskal Wallis one-way based on their normal or not-normal distribution, respectively (normality of the distribution of variables was tested by the Kolmogorov Smirnov test). Categorical variables were tested with the chi-square test.

Univariate binary logistic regression was used to evaluate predictors of PCa and high-grade PCa. A multivariate binary logistic regression model was developed with the statistically significant variables. Low-grade disease was defined as Gleason 6 and high-grade disease as Gleason ≥7 as defined by the mobile apps. Receiver operator characteristic curves (ROCs) were produced to evaluate the area under the curve (AUC) and the diagnostic performance of the App. Performance characteristics of the app were assessed by calibration plots, where the x axis represents the predicted probability, and the y axis represents the actual observed accuracy of the biopsy. Significance of an observed miscalibration was tested via the Hosmer Lemeshow test. For this test, a p value < 0.05 indicates a poor agreement between predicted probabilities and observed outcome. Decision curves were generated to evaluate the net benefit of the App.

Results

Overall, 580 patients with a median age of 66 (61/70) years were enrolled in eleven Italian centers. Median PSA was 6 (4/8) ng/ml and median prostate volume was 47 (39/61) ml. Median BMI was 27 (25/29) kg/m^2. Patients' characteristics are shown in Table 1. Moreover, 178/580 (31%) had previous biopsies. mpMRI showed the following PIRADS scores: 26 (4.5%) PIRADS 1, 2 (0.4%) PIRADS 2, 196 (33.8%) PIRADS 3, 263 (45.3%) PIRADS 4 and 93 (16%) PIRADS 5.

Overall, 404/580 (70%) presented PCa. These patients were older, presented higher PSA levels, lower prostate volumes and a higher proportion of PIRADS score >3 when compared to patients with negative biopsies (Table 1). On uni and multivariate logistic regression analysis age, PSA, DRE, PV and PIRADS score >3 were independent predictors of PCa (Table 2). The RPCRC app presented good discrimination (AUC = 0.74), fair calibration and a clinical net benefit in the range of probabilities between 50 and 90% for the prediction of PCa (Fig. 1).

Overall, 224/580 (38%) presented high-grade PCa. These patients were older, presented higher PSA levels, lower prostate volumes and a higher proportion of PIRADS score>3 when compared to patients with no/low grade PCa (Table 1). On uni and multivariate logistic regression analysis age, PSA, DRE, PV and PIRADS score>3 were independent predictors of high-grade PCa (Table 2). In the prediction of high-grade PCa, the RPCRC app presented good discrimination (AUC = 0.79), good calibration (p = 0.48) and a clinical net benefit in the range of probabilities between 20 and 80% (Fig. 1).

Table 1
Patients' characteristics according to presence/absence of cancer and his grade.

	Overall	No PCa	PCa	p	Low Grade/No Cancer	High-Grade	p
N° of patients	580	176/580 (30%)	404/580 (70%)		356/580 (62%)	224/580 (38%)	
Age (years)	66 (61; 70)	65; 59/70	67; 62/71	.001	64 (60; 68)	67 (63; 71)	0.001
PSA (ng/ml)	6 (4; 8)	6 (4/8)	7 (5/9)	.001	5 (4; 8)	7 (5; 9)	0.001
BMI (kg/m^2)	27 (25; 29)	27; 25/29	27; 25/29	.475	26 (25; 28)	27 (25; 29)	0.475
PV (ml)	47 (39; 61)	52; 40/70	45; 35/52	.001	48 (40; 61)	45 (36; 60)	0.001
PIRADS score >3	365/580 (63%)	46/176 (26%)	319/404 (78%)	.001	166/356 (47%)	190/224 (85%)	0.001

Data are presented as median (interquartile range); PSA: prostate specific antigen, DRE: digital rectal examination; BMI: body mass index.
PV:prostate volume, PCa: prostate cancer.

Table 2
Uni-variate and Multi-variate binary logistic regression analysis for the risk of PCa and high-grade PCa.

	PCa risk				High-grade PCa risk			
	Uni-variate	p	Multi-variate	p	Uni-variate	p	Multi-variate	p
Age	1,07 (1,05-1,11)	0,01	1,05 (1,01-1,09)	0,01	1,08 (1,05-1,11)	0,01	1,06 (1,03-1,10)	0,01
PSA	1,03 (1,01-1,05)	0,01	1,04 (1,01-1,06)	0,01	1,09 (1,04-1,14)	0,01	1,09 (1,04-1,15)	0,01
DRE	2,24 (1,48-3,39)	0,01	1,68 (1,05-2,68)	0,03	2,53 (1,77-3,63)	0,01	1,87 (1,26-2,80)	0,01
BMI	1,23 (0,87-1,58)	0,15			1,56 (1,34-1,90)	0,54		
PV	0,97 (0,95-0,99))	0,02	0,98 (0,96-0,99)	0,01	0,98 (0,97-0,99)	0,03	0,98 (0,97-0,99)	0,01
PIRADS score >3	9,32 (6,20-14,01)	0,01	8,09 (5,33- 12,28)	0,01	6,40 (4,20-9,74)	0,01	5,1 (3,35-8,03)	0,01

PSA: prostate specific antigen, DRE: digital rectal examination; BMI: body mass index; PV: prostate volume, PCa: prostate cancer.

Discussion

The present study successfully validates the new version of the Rotterdam mobile phone App in a multicenter Italian cohort of patients at increased risk of PCa. More specifically the App presented very good discrimination abilities in the prediction of PCa and high-grade PCa. Moreover, we confirm the important role of Age, DRE, PSA, PV and PIRADS score in the prediction of PCa and high-grade PCa. Our results are in line with the peer-reviewed literature and confirm the internal validity of our results [20] [–] [23].

Mobile phone health apps are increasingly gaining attention in oncological care [24]. These apps represent potential tools in the diagnosis of malignancies or to support cancer patients [25]. Apps have been widely used by professionals and patients, and attention to them in health care environments is increasing daily [26]. However, developing a health mobile app available to the public carries the risk of releasing a dangerous app that can induce people to over- or under-estimate their health issue. Therefore, it is fundamental to use only validated tools developed from validated studies of high scientific value.

The RPCRC, previously only available digitally on the website and now as a mobile App, was based on the Rotterdam arm of the ERSPC, which started in 1993 in Europe to study the feasibility of a population-based screening for PCa and its effect on mortality [27]. This app is publicly available on the Apple App Store and on Android Google Play Store at the cost of 2.29 € and 1.79 €, respectively [19]. A recent study of our group has evaluated the previous version of this mobile app [5], showing a fair accuracy in the prediction of PCa. In the present study, we used this App in 580 patients enrolled in different Italian Regions. According to our results, the new RPCRC app presented a good discrimination, fair calibration and a clinical net benefit in the range of probabilities between 50 and 90% for the prediction of PCa. Moreover, in the prediction of high-grade PCa, the RPCRC app presented a good discrimination, good calibration and a clinical net benefit in the range of probabilities between 20 and 80%. The fair calibration of the cancer model clearly depends on the enrolled population which is different from the development cohort specially regarding cancer prevalence. In our population the app overestimates the risk of cancer in the range of probabilities between 65 and 85% (Fig. 1b). It is important to underline that the App is easy to use either for urologist or for the public, easy to access (available on App Store and Google Play Store) and cheap.

In the recent years some authors have evaluated the risk calculator in different populations. In the development cohort, Alberts et al. found an AUC of 0.83 for the prediction of cancer and an AUC of 0.84 for high-grade cancer for the ERSPC-RC3 [8,28]. Very recently, Pullen et al. validated the ERSPC-R3/4 calculator in a small German cohort of 307 patients finding an AUC of 0.82 for the prediction of cancer. However the authors did not perform an evaluation for the risk of high-grade cancer. This small study has the limitation that the validation is performed only for cancer detection while no data on high-grade PCa is available and moreover this study did not consider that, when different prevalence occurred, the intercept has to be adjusted for a correct risk assessment. Thereafter some authors have evaluated the best strategy in patients at risk of PCa.

Falagario and coworkers evaluated 266 biopsy-naïve patients who underwent mpMRI, the 4Kscore test, and prostate biopsy to define the best strategy to avoid unnecessary testing and biopsies. They found that the most clinically beneficial biopsy strategy was an initial 4Kscore test followed by mpMRI if the 4Kscore was >7.5% and a subsequent biopsy if the mpMRI was positive or 4Kscore was >18%. They concluded that Physicians should consider clinical risk screening tools when ordering and interpreting mpMRI results to avoid unnecessary procedures and diagnostic errors.

Overall risk calculators and mobile phone apps for the prediction of cancer represent an interesting area of research.

The RPCRC has shown in our experience an important clinical net benefit in predicting high-grade PCa as shown by the decision curve analysis. Moreover, its clinical utility is shown in a broad range of probabilities (20–80%). These excellent results should encourage the use of this app in every day clinical practice. The role of this app in patients' counseling and decision process should be further investigated in clinical trials.

The main limitation of these models is the lack of studies evaluating their implementation in clinical practice. Many models are developed and validated but very rarely used in every day clinical practice. Moreover, an important limitation of PCa models is the

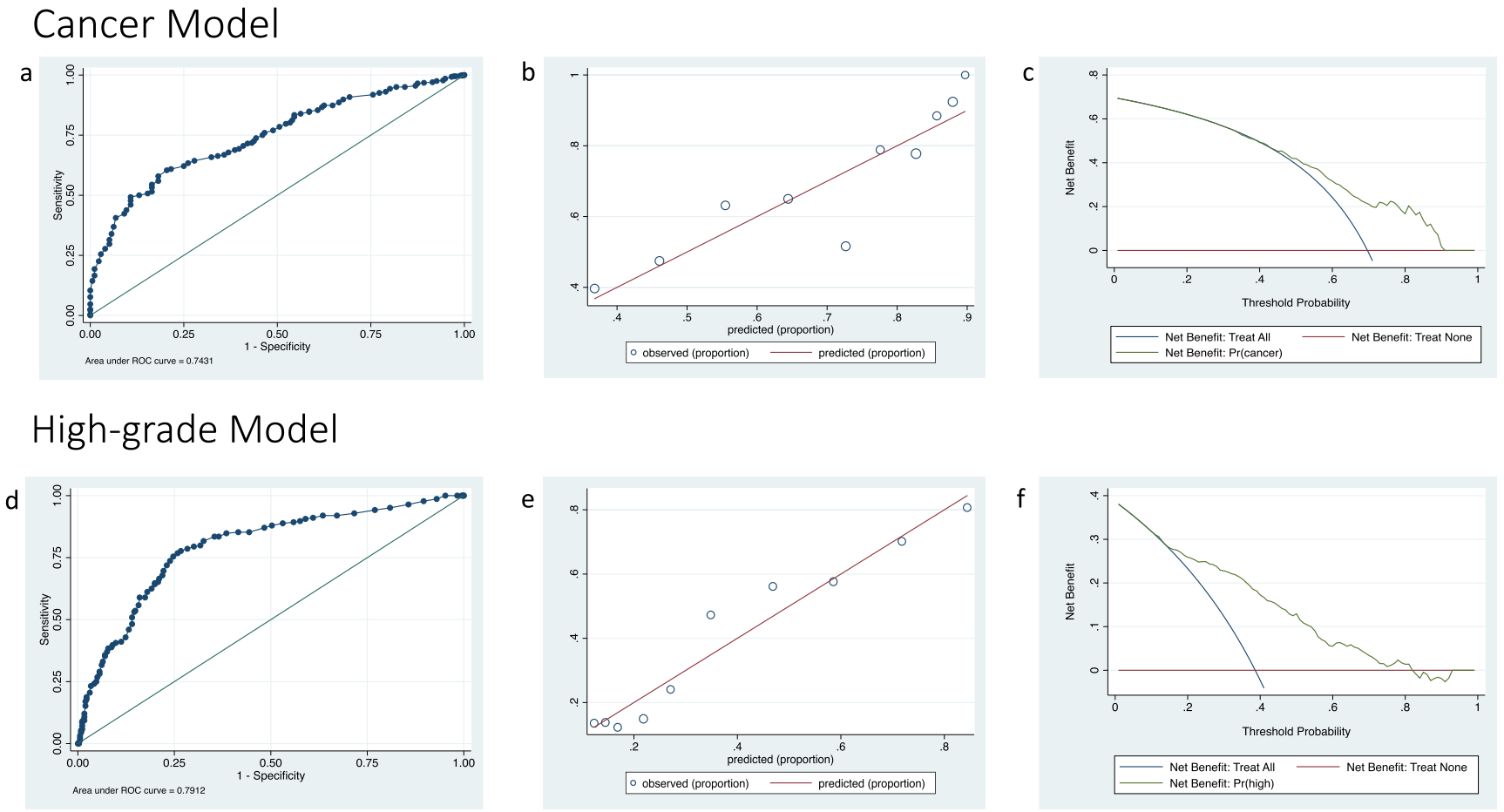

Fig. 1. Performance of cancer model and high-grade model according to receiver operator characteristic curve (a and d), calibration plots (b and e) and decision curve analysis (c and f).

lack of a cut-off to decide not to perform prostate biopsies. The Rotterdam PCRC suggest not to perform prostate biopsies if the risk is less than 12% however, we still not know if a 10% risk of cancer is acceptable for the patient. Probably it is very difficult for patients to make a decision on a probability, especially when speaking about cancer. A study to evaluate patient perception when using the app to decide to perform prostate biopsies is ongoing and results will be soon available.

We must acknowledge several limitations of our study. First of all, this is an Italian eleven-centers experience, so the results clearly depend on the enrolled population. We validated the app in a highly selected population of patients with positive mpMRI (PIRADS≥3: 95%) which resulted in a high prevalence of cancer (70%). However our results are in line with the available evidence on patients with PIRADS score ≥3 [20]. We certainly acknowledge that it takes more than one study and one cohort of patients to prove a hypothesis. PCa epidemiology presents large differences due to racial and geographical issues that need to be explored. We have performed the study in a southern European cohort of patients that may be different from northern European, North American, South American and Asian populations [29]. Another limitation, common to most studies in this area, derives from the use of biopsy cohorts without confirmation by radical prostatectomy specimens. Furthermore, we did not compare the mobile App results with the online calculator. Another possible limitation to consider in our study is lack of information about the Prostate Health Index (PHI), due to difficulties to find the p2PSA test. Moreover, a possible limitation, common to other studies that include mpMRI, is the variability in mpMRI results due to the different machines used and the Radiologist experience in this new diagnostic modality of clinically significant PCa.

Notwithstanding all these limitations, our study is the first available validation of the new version of RPCRC mobile App with the result adjusted for the PCa prevalence as described in the methods section. When this model is adapted to the group prevalence it may represent an optimum balance between saving unnecessary biopsies and missing clinically significant PCa. The risk calculators are dependent on the prevalence of clinically significant PCa and therefore may not deliver optimal accuracy of PCa prediction if used in clinical settings where there is a large difference in prevalence between the clinical cohort and the original cohorts [8]. In our opinion this Mobile App can be considered a useful tool for assisting physicians and patients in the individual risk assessment in patients at risk of prostate cancer; to discuss the pros and cons of a prostate biopsy and to define a possible acceptable threshold for follow-up strategy.

Conclusions

In our experience the RPCRC App is an excellent tool to help physicians to individualize prostate cancer risk and to better discuss the pros and cons of a prostate biopsy with the patients. Its implementation in clinical practice could further define its role in the management of patients at risk of prostate cancer and particularly of high-grade cancer. Future studies should evaluate its routinely use and its application in different populations at different risk of PCa.

CRediT authorship contribution statement

Cosimo De Nunzio: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Riccardo Lombardo:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Valeria Baldassarri:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Luca Cindolo:** Conceptualization, Data curation, Formal analysis, Writing – review & editing. **Riccardo Bertolo:** Conceptualization, Data curation, Formal analysis, Writing – review & editing. **Andrea Minervini:** Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft. **Francesco Sessa:** Conceptualization, Visualization, Writing – review & editing. **Gianluca Muto:** Conceptualization, Supervision, Validation, Visualization, Writing – review & editing. **Pierluigi Bove:** Conceptualization, Supervision, Validation, Visualization, Writing – original draft. **Matteo Vittori:** Conceptualization, Data curation, Formal analysis, Writing – review & editing. **Giorgio Bozzini:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing. **Pietro Castellan:** Conceptualization, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing. **Filippo Mugavero:** Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Mario Falsaperla:** Conceptualization, Data curation, Formal analysis, Resources, Supervision, Writing – review & editing. **Luigi Schips:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Writing – review & editing. **Antonio Celia:** Conceptualization, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Maida Bada:** Conceptualization, Data curation, Formal analysis, Validation, Visualization, Writing – original draft. **Angelo Porreca:** Validation, Visualization, Writing – original draft, Writing – review & editing. **Antonio Pastore:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Yazan Al Salhi:** Conceptualization, Data curation, Formal analysis, Investigation, Writing – review & editing. **Marco Giampaoli:** Conceptualization, Data curation, Writing – review & editing. **Giovanni Novella:** Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Riccardo Rizzetto:** Conceptualization, Data curation, Formal analysis, Writing – review & editing. **Nicolo Trabacchin:** Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Guglielmo Mantica:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Giovannalberto Pini:** Conceptualization, Data curation, Validation, Visualization, Writing – original draft, Writing – review & editing. **Sebastiaan Remmers:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Alessandro Antonelli:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Andrea Tubaro:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

No conflict of interest declared.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for profit sectors. This research involves Human Participants, it does not involve animals and every patient enrolled have signed an informed consent.

Acknowledgements

None.

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