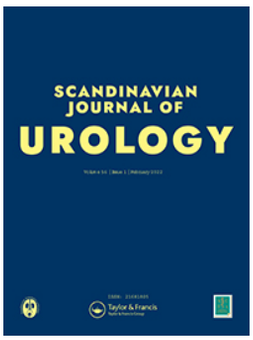

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ARTICLE

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A prospective multicenter study of visual response-evaluation by cystoscopy in patients undergoing neoadjuvant chemotherapy for muscle invasive urinary bladder cancer

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ABSTRACT

Purpose: To evaluate a method of transurethral visual response-staging in patients with urothelial muscle-invasive urinary bladder cancer (MIBC), undergoing neoadjuvant chemotherapy (NAC) and radical cystectomy (RC).

Methods: A prospective study at four Swedish cystectomy centers, cystoscopy was performed after final NAC-cycle for MIBC. Fifty-six participants underwent cystoscopy for visual staging of the tumor immediately pre-RC. Visual assessments were correlated to pathoanatomical outcomes post-RC.

Results: Seventeen tumors were classified as complete response (CR), i.e. pT0. Twenty-five patients had residual MIBC and 14 had non-muscle invasive residual tumors (NMIBC). Of the 39 patients with residual tumor, 25 were correctly identified visually (64%). Eleven patients were pN+. The diagnostic accuracy of cystoscopy to correctly identify complete response or remaining tumor was 70% (CI = 56–81%) with a sensitivity of 64% (CI = 47–79%), specificity 82% (CI = 57–96%), PPV 89% (CI = 74–96%) and NPV 50% (CI =38–61%). Twenty-eight cystoscopy evaluations showed signs of residual tumors and 3/28 (11%) were false positive. In 4/14 patients assessed having residual NMIBC the estimates were correct, 8/14 had histopathological MIBC and 2/14 had CR. In 11/14 patients (79%), the suggested visual assessment of MIBC was correct, 2/14 had NMIBC and 1/14 had CR. Twenty-eight cystoscopies had negative findings, 14 were false negatives (50%), when cystoscopy falsely predicted pT0. Among them there were eight patients with pTa, pT1 or pTis and six MIBC-tumors. In 17 patients with histopathological pT0, 14 were correctly identified with cystoscopy (82%).

Conclusion: Cystoscopy after the final NAC-cycle cannot robustly differentiate between NAC-responders and non-responders. Visually, negative MIBC-status cannot be determined safely.

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Cystectomy; neoplasm staging; neoadjuvant therapy; urinary bladder neoplasms

Introduction

Bladder cancer is the ninth most common cancer worldwide and ranks 13th in terms of deaths, with smoking as its major risk factor [1,2]. In approximately one-quarter of the patients the cancer is muscle-invasive [3]. The most recent Swedish bladder cancer statistics display an increased incidence but yet improved survival and a stable mortality [4]. The treatment alternatives today depend on the tumor staging, clinical staging, patient age and comorbidity and vary from transurethral resection (TURb) only, radical surgery to local or systemic chemotherapy or a combination of them all [3]. Local control with chemotherapy instillations, immunotherapy with BCG-instillations and repeat TURb are some of the treatment recommendations for non-muscle invasive bladder cancer. The gold standard treatment for muscle-invasive bladder cancer is radical cystectomy (RC) preceded by neoadjuvant chemotherapy (NAC) in fit and eligible patients [3].

The prognosis of urothelial muscle-invasive bladder cancer (MIBC) is relatively poor with a 5-year survival around 50% for all clinical stages T2–T4 following RC [3]. Cisplatin-based neoadjuvant combination NAC significantly increases survival for a chemo-sensitive sub-group of these patients, with an absolute risk reduction (ARR) of 31% for death in completely downstaged patients (pT0N0M0) at 5 years median observation time, compared to cystectomy only patients with complete downstaging [5]. In the original randomized prospective Nordic intention-to-treat-studies, the increased overall survival (OS) in the experimental arm was 8% compared to the control arm [6] and, in a systematic review and

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meta-analysis of ten randomized trials ($n = 2{,}688$), the OS was increased by 5% at median observation time of 5 years [7].

In the last 10 years, since the national introduction of NAC in Sweden, an increasing frequency of hospitals in Sweden have started to implement NAC for MIBC-patients. The most common alternatives for chemotherapy are either a combination of methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) given in three-to-four cycles or gemcitabine and cisplatin/carboplatin (GC) for a total of three-to-four cycles [8]. Inclusion criteria for NAC, according to the Swedish guidelines, are biological age $\leq$ 75 years and intact renal function with GFR $>$ 55–60 plus an acceptable comorbidity. For unfit patients, the standard recommendation is traditional cystectomy as radical treatment, if fit for major surgery. MIBC-patients unfit for any radical surgery are instead offered radical full dose radiation. A small percentage of MIBC-patients who, for medical reasons, are unfit for both surgery or radiation are offered other local options for symptomatic treatment and in some instances a combined oncological approach.

For non-responders to NAC, there will be a cystectomy-delay, in which the patients risk receiving largely ineffective treatment for 2.5–3 months prior to radical surgery. Retrospective studies evaluating the outcomes of NAC in regard of residual bladder cancer have reconfirmed that patients with downstaged tumors following NAC and RC have significantly improved survival projections compared to non-responders [9–11]. These findings confirm the results of the post hoc analysis of the Nordic combined randomized prospective trials [5]. Yet, the urological community still lacks solid and reliable markers and methods to early identify complete responders to NAC. Early and robust identification of responders and non-responders, respectively, could enable alternative treatment options for the latter group at an early point of time, thus, saving non-responders from a treatment with low efficacy and further avoiding the risks of side effects and complications to NAC [12]. Different research groups have therefore attempted to establish methods to predict the effects of NAC, in differentiating responders versus non-responders as early as possible in the clinical process, but yet without robust and validated results translating into clinical practice or recommendations [13–16]. A recently published study evaluated biomarkers from the two randomized prospective cystectomy trials, NCS 1 & 2 [6]. Utilizing immunohistochemistry on pretreatment tumor specimens and clinical data in 250 patients, the study focused on four biomarkers; CCTα, emmprin, survivin, and BCL-2. In conclusion, only CCTα provided some predictive information for NAC-response, which was improved by adding one of the other three markers, preferably emmprin. Yet, due to insufficient statistical power the suggested markers cannot be translated yet to clinical practice, and the study warrants additional trials and further validation [17].

For cystoscopic visual staging of newly diagnosed bladder tumors, accuracy of the method showed, in a single center retrospective study from the UK in 2016, that assessment predictions of MIBC had a sensitivity of 88.9% and a specificity of 91.0%, resulting in a positive predictive value of 78.4% and a negative predictive value of 95.7%. Thus, visual staging is an option up for evaluation [18]. The value of visual staging in newly diagnosed bladder tumors was also shown in a prospective double-blind clinical study from 2017. In 224 enrolled patients, NMIBC and MIBC were predicted accurately in 93.4% and 85.2%, respectively [19]. Yet so far there is only one group that has published a study on visual staging *per se*, pre-RC and post-NAC, performed by

Table 1. Patient characteristics, staging after TUR-b and cystectomy and details on administered neoadjuvant chemotherapy (NAC).

Patient characteristics categorical variables	*N* (%)
Sex	
Female	14 (25)
Male	42 (75)
Year of cystectomy	
2015	5 (9)
2016	2 (4)
2017	11 (20)
2018	11 (20)
2019	11 (20)
2020	9 (16)
2021	7 (13)
Cystectomy center	
Linköping	5 (9)
Uppsala	8 (14)
Sundsvall	5 (9)
Umeå	38 (68)
Histopathology	
Urothelial	48 (86)
Urothelial, micropapillary	2 (4)
Urothelial, adenomatous	1 (2)
Urothelial, neuro-endocrine	1 (2)
Urothelial, squamous cell	1 (2)
Urothelial, sarcomatoid	1 (2)
Urothelial, nested variant	2 (4)
cT-stage	
T2	43 (77)
T3	12 (21)
T4a	1 (2)
pT-stage	
T0	17 (30)
Ta, Tis, T1	14 (25)
T2	12 (21)
T3	9 (16)
T4a	3 (5)
T4b	1 (2)
pN-stage	
NX	1 (2)
N0	44 (79)
N1	3 (5)
N2	8 (14)
pM-stage	
M0	56 (100)
M1	0 (0)
Radicality of primary urinary bladder specimen	
Radical	53 (95)
Unradical	1 (2)
ND	2 (4)
NAC treatment	
MVAC-HD	48 (86)
MVAC	2 (4)
Cisplatin-Gemcitabine	5 (9)
Carboplatin-Gemcitabine	1 (2)
Number of NAC-cycles	
Two cycles	6 (11)
Three cycles	45 (80)
Four cycles	4 (7)
Six cycles	1 (2)
Patient characteristics continuous variables	Median [IQR]
Age	70 [63–73]

Table 2. Visual cystoscopy assessments over dichotomous pathoanatomical assessments of NAC-responses post-RC.

	Cystoscopy: negative	Cystoscopy: residual cancer
pT0: Complete response	14 (50) True negative	3 (11) False positive
≥pT1: Not complete response	14 (50) False negative	25 (89) True positive

Data are shown as *n* (%).

Table 3. Cystoscopy assessment after the final treatment with neoadjuvant chemotherapy (NAC) and assessment of NAC-response groups after cystectomy of the 56 study cases.

	Cystoscopy: negative	Cystoscopy: residual cancer
Complete response [pT0]	14 (50)	3 (11)
Partial response [pTis or T1]	8 (29)	6 (21)
Stable disease [pT2, pT3 or pT4a]	4 (14)	11 (39)
Progressive disease [pN1-2 or pT4b]	2 (7)	8 (29)

Data are shown as *n* (%).

cystoscopic examination following the second cycle of NAC [20]. The study from Mansour et al. [20] showed an OR of 7.79, in the multivariate analysis, in favor of visual staging as a predictor of downstaging. In the study, only 16% of the patients had received the chemotherapy combination MVAC and 84% had received cisplatin-gemcitabine as NAC-treatment. The analysis was performed in a retrospective manner on prospectively collected data. Cystoscopic images were saved from the initial TURb, and later also after the second cycle of NAC. In addition, bimanual palpation was performed in conjunction with the cystoscopies [20]. In a recently published study evaluating clinical restaging and tumor sequencing, 114 patients underwent restaging TUR following NAC prior to RC. In total, 53% had no evidence of disease (pT0) on post-NAC TUR, yet, from these, only 47% were pT0 on final RC pathology. Among patients with no visual evidence of residual disease on white light cystoscopy ($n = 88$), TUR was performed in 21. Only 81% ($n = 17$) in that sub-cohort were true pT0. In the seventeen patients, 41% had residual tumor on post-RC pathology, including four with pT2 tumors. Thus, the study highlights the dilemma of using clinical staging for evaluation of NAC-responses in MIBC [21].

We intended to evaluate the concept of visual staging as a method for response evaluation to NAC-therapy, in a prospective cohort of MIBC-patients planned for radical cystectomy. The primary aim was to calculate the diagnostic accuracy of cystoscopy to find recurrent tumor and a secondary aim was to assess if visual staging could differentiate between MIBC and NMIBC.

Materials and methods

Design and patients

The study was designed as a prospective pilot investigation.

From May 2015 until April 2021, 56 patients at seven Swedish urological centers were prospectively enrolled, primarily from time of TURb: Norrlands University Hospital, Skellefteå county Hospital, Sundsvall/Härnösand county Hospital, Nyköping county Hospital, Uppsala University Hospital, Norrköping county Hospital and Linköping University Hospital and further cystectomized at four of the mentioned centers. Inclusion criteria were patients with urothelial muscle-invasive cancer, staged cT2-T4aN0M0, receiving NAC prior to RC and giving formal consent to participate. Exclusion criteria were patients with urothelial muscle invasive cancer undergoing RC without NAC or patients undergoing NAC but unwilling to participate.

The mean age was 67 years and the median age 70 years (range = 39–80) at the time of diagnosis. Forty-two males and 14 females were included (Table 1). The patients were also included in a larger prospective translational study investigating tumor immunology and tumor biological mechanisms, with focus on primary tumor, sentinel node detection, draining and non-draining regional lymph nodes [22–28].

All included patients had undergone standard clinical practices with an initial transurethral resection of the bladder tumor for primary staging plus CT-evaluations with contrast enhancement.

The TURB-Ts of all included patients were considered as being macroscopically radical and were performed by senior subspecialized bladder cancer urologists in our national research team. After the final NAC-cycle, just prior to the cystectomy, all patients were evaluated with cystoscopy in the OR by a senior specialist in urology at each participating center. The evaluator was always subspecialized in surgical treatment of urinary bladder cancer and a member of the local bladder cancer/cystectomy-team of the center performing RC. The urologists in the national research group for this study have together standardized the evaluation criteria. Following the pre-RC cystoscopy, the urologist evaluator filled a case report form (CRF) indicating if visual residual cancer could be seen or not. If residual cancer was seen, the urologist estimated if the cancer was likely to be muscle invasive (MIBC) or not (NMIBC). Bimanual palpation, considered as being a confounding factor for the visual assessment, was intentionally excluded from the investigation.

Chemotherapy, surgical technique and histopathology

Most of the patients (86%) received MVAC-HD and mainly three cycles of NAC were delivered according to local and regional oncological routines. In Sweden, MVAC-HD is the most preferred treatment combination for NAC by the medical oncologists and cisplatin-gemcitabine is the first choice in only one national center (Table 1). All patients underwent radical cystectomy with sentinel node dissection and with the intended extent of including the following stations:

Table 4. Visual staging and response to NAC in each participating patient.

Patient number	pT	pN	Visual residual cancer	pT0 visual true	Visual residual cancer true
1	pT0	pN0	No	Yes	
2	pT4a	**pN2**	Yes		Yes
3	pT4b	pNX	Yes		Yes
4	pT0	pN0	No	Yes	
5	pT2	**pN1**	Yes		Yes
6	pT3a	pN0	Yes		Yes
7	pT4a	pN0	Yes		Yes
8	pTis	pN0	Yes		Yes
9	pT3a	**pN2**	Yes		Yes
10	pT1	pN0	No	No	
11	pT0	pN0	No	Yes	
12	pT0	pN0	No	Yes	
13	pTis	pN0	No	No	
14	pT2	pN0	Yes		Yes
15	pT0	pN0	No	Yes	
16	pT2	pN0	Yes		Yes
17	pT2	**pN1**	Yes		Yes
18	pT0	pN0	Yes		No
19	pT3b	**pN2**	No	No	
20	pT0	pN0	Yes		No
21	pT2b	N0	Yes		Yes
22	pT3	pN0	Yes		Yes
23	pT3a	**pN1**	Yes		Yes
24	pT1	pN0	No	No	
25	pT0	pN0	No	Yes	
26	pT2	**pN2**	Yes		Yes
27	pT0	pN0	No	Yes	
28	pT3	pN0	Yes		Yes
29	pT3	**pN2**	Yes		Yes
30	pT0	pN0	No	Yes	
31	pT2b	pN0	No	No	
32	pT0	pN0	No	Yes	
33	pT3	**pN2**	No	No	
34	pTis	pN0	No	No	
35	pTis	pN0	No	No	
36	pTis	pN0	Yes		Yes
37	pT2a	pN0	Yes		Yes
38	pTis	pN0	No	No	
39	pT2	pN0	Yes		Yes
40	pT0	pN0	No	Yes	
41	pT1	pN0	Yes		Yes
42	pT4a	**pN2**	Yes		Yes
43	pTaG3	pN0	Yes		Yes
44	pT0	pN0	No	Yes	
45	pT0	pN0	Yes		No
46	pT2	**pN2**	No	No	
47	pT1	pN0	Yes		Yes
48	pT3	pN0	Yes		Yes
49	pT2	pN0	No	No	
50	pT1	pN0	Yes		Yes
51	pT0	pN0	No	Yes	
52	pTis	pN0	No	No	
53	pT0	pN0	No	Yes	
54	pTaG3	pN0	No	No	
55	pT2	pN0	No	No	
56	pT0	pN0	No	Yes	
Number of Yes			28	14	25
Number of No			28	14	3

Bilateral Obturator fossae, External Iliac artery bilaterally and Common Iliac arteries up to mid-level [22].

Statistical analyses

All data from the CRFs, including clinical information on patients' age, gender, tumor staging clinically/visually and pathologically, type and number of NAC-cycles and days from last NAC to radical cystectomy were gathered in an SPSS 26 file (SPSS, Chicago, IL). Descriptive statistics were used to present data. Median values with interquartile range (IQR) were reported. The diagnostic accuracy of cystoscopy was assessed with sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). Point estimates were presented with 95% confidence intervals (CI) based on the clopper Pearson (exact) method.

Results

For baseline characteristics and staging-procedures after TUR-B (cTNM) and after cystectomy (pTNM) see Table 1. All patients received neoadjuvant chemotherapy (NAC) and MVAC-HD was the most common regimen ($n = 48$). Two-to-

Table 5. Results of the visual estimates of residual cancer, distributed over visual MIBC resp. visual NMIBC.

Patient no.	pT	pN	Visual residual estimate	Visual residual estimate of any cancer	Visual residual estimate of MIBC: True	Visual residual estimate of NMIBC: True
1	pT0	pN0	/			
2	pT4a	**pN2**	pT2	Yes	Yes	
3	pT4b	pNX	pT2	Yes	Yes	
4	pT0	pN0	/			
5	pT2	**pN1**	pT2	Yes	Yes	
6	pT3a	pN0	pT2	Yes	Yes	
7	pT4a	pN0	pT2	Yes	Yes	
8	pTis	pN0	pTa–T1	Yes		Yes
9	pT3a	**pN2**	pTa–T1	Yes		No
10	pT1	pN0	/			
11	pT0	pN0	/			
12	pT0	pN0	/			
13	pTis	pN0	/			
14	pT2	pN0	pTa-T1	Yes		No
15	pT0	pN0	/			
16	pT2	pN0	pTa-T1	Yes		No
17	pT2	**pN1**	pT2	Yes	Yes	
18	pT0	pN0	pT2	Yes	No	
19	pT3b	**pN2**	/			
20	pT0	pN0	pT1–T2	Yes		No
21	pT2b	N0	pT2–T3	Yes	Yes	
22	pT3	pN0	pT2	Yes	Yes	
23	pT3a	**pN1**	pT1–T2	Yes	Yes	
24	pT1	pN0	/			
25	pT0	pN0	/			
26	pT2	**pN2**	pT1	Yes		No
27	pT0	pN0	/			
28	pT3	pN0	pT1	Yes		No
29	pT3	**pN2**	pT1	Yes		No
30	pT0	pN0	/			
31	pT2b	pN0	/			
32	pT0	pN0	/			
33	pT3	**pN2**	/			
34	pTis	pN0	/			
35	pTis	pN0	/			
36	pTis	pN0	pT2	Yes	No	
37	pT2a	pN0	pT2	Yes	Yes	
38	pTis	pN0	/			
39	pT2	pN0	pT1	Yes		No
40	pT0	pN0	/			
41	pT1	pN0	pT1	Yes		Yes
42	pT4a	**pN2**	pT1	Yes		No
43	pTaG3	pN0	pT1	Yes		Yes
44	pT0	pN0	/			
45	pT0	pN0	pT1	Yes		No
46	pT2	**pN2**	/			
47	pT1	pN0	pT1	Yes		Yes
48	pT3	pN0	pT2	Yes	Yes	
49	pT2	pN0	/			
50	pT1	pN0	pT2	Yes	No	
51	pT0	pN0	/			
52	pTis	pN0	/			
53	pT0	pN0	/			
54	pTaG3	pN0	/			
55	pT2	pN0	/			
56	pT0	pN0	/			
Number of Yes				28	11	4
Number of No					3	10
Total Number					14	14

In 28/56 patients there were evaluations performed regarding the visual staging of actual residual tumor. In 3/14 patients with visual staging being *residual MIBC*, the estimates were incorrect; two patients had NMIBC and one had CR.
In 4/14 patients with visual staging being residual NMIBC, the estimates were correct, 8/14 had MIBC and 2/14 were completely downstaged to pT0.

six NAC cycles were given and 45 patients received three cycles. Post-cystectomy, 12 patients were classified as complete responders (CR), i.e. pT0. Twenty-five patients had residual MIBC locally and 14 had non-muscle invasive residual tumors (NMIBC). Eleven patients had lymph node metastases (Table 1).

The analysis of diagnostic accuracy of cystoscopy to correctly identify complete response or remaining tumor was 70% (CI = 56–81%) with a sensitivity of 64% (CI = 47–79%), specificity 82% (CI = 57–96%), PPV 89% (CI = 74–96%) and NPV 50% (CI = 38–61%). In 28/56 patients (50%) the visual staging was pT0 and in the remaining half the visual staging was *any residual cancer*. Three of the 28 cystoscopies with residual cancer were false positive (11%) (Tables 2 and 3). The visual staging of pT0 was false in 14/28 patients (50%). The false predictions of pT0 ($n = 14$) were distributed over

true MIBC-patients as 6/14 and over true NMIBC-patients as 8/14. Of the 17 patients with actual pT0, 14 were correctly identified with a negative cystoscopy (82%) and of the 39 patients with actual residual tumor, 25 were correctly identified with a positive cystoscopy (64%). For further individual level data on cystoscopy findings, T- and N-stages (Table 4).

In 28/56 patients (50%) there were evaluations performed regarding the visual staging of actually residual tumor. In 3/14 patients (21%) with visual staging being residual MIBC, the estimates were incorrect; two had NMIBC and one had CR. In 4/14 patients with visual staging being residual NMIBC, the estimates were correct, 8/14 had MIBC and 2/14 had CR (Table 5).

Discussion

The optimal long-term survival treatment for MIBC is yet to be found. Even though NAC has been a successful addition, in terms of improved OS, for a substantial number of patients since the introduction, yet there is a significant proportion of non-responders [5–6].

One major problem with NAC is to early differentiate responders to treatment from non-responders. Patients with non-responding tumors risk undergoing substantial delays in treatment with an increased risk of dissemination in the course of time.

The Mansour trial suggested that, after the second NAC cycle, cystoscopy could be performed routinely for identifying responders versus non-responders to NAC [20]. The investigators based their conclusions on registering that there were a significantly higher percentage of visually observed pT0 stages among responders to cisplatin-gemcitabine chemotherapy compared to what was found in non-responders; 36.5% versus 2.5%. This correlated with significantly better survival rates in the responder group.

In our study the patients had mainly received HD-MVAC chemotherapy instead of cisplatin-gemcitabine as in the Mansour-study. Mansour et al. performed the cystoscopy routinely after the second cycle of NAC, while the patients in our study were examined after the last cycle of NAC, mainly after the third cycle. Our study was performed prospectively and the possible confounder of bimanual palpation was excluded in conjunction with the cystoscopy. In contrast to the Mansour study, the same surgeon had not performed the cystoscopy on all the patients in our study. Although the visual evaluators were always subspecialized in surgical treatment of urinary bladder cancer, and members of the local bladder cancer-teams, there is of course a risk of interindividual bias. In our complete cohort of 56 patients, 14 patients were false negative at cystoscopy with 43% (6/14) turning out to have MIBC. Thus, if visual evaluation, as a clinical marker of response/non-response, would have been utilized for therapy choices in a real clinical setting, more than a third of the patients with FN cystoscopy would have been considered as successful NAC responders – yet being complete non-responders with remaining MIBC. Further, in as much as 8/14 patients had estimated visual NMIBC, the final histopathology post-RC revealed MIBC (non-response).

The strength of the study is the prospective design in a multicenter setting. However, the number of patients were low and larger sufficiently powered cohorts are needed to verify the results.

We conclude that cystoscopy after the final NAC-cycle could not robustly differentiate between NAC-responders and non-responders in this prospective pilot study. Visually, negative MIBC-status could not be determined safely and to utilize visual staging as part of response/non-response evaluations in patients with MIBC undergoing NAC seems to be of no clinical and predictive value.

Ethical approval

The study was approved by the Regional Ethics Board in Stockholm, dnr: 2007/71-31/2. The study conforms to the provisions of the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013).

Informed consent

All included patients gave their oral and written consent to participate.

Consent for publication

All included patients gave their oral and written consent for the study to be published.

Author contributions

Protocol/project development: Amir Sherif, Danna Asad, Firas Aljabery. Data collection or management: Amir Sherif, Danna Asad, Firas Aljabery, Mohammad Hagsheno, Markus Johansson, Ylva Huge, Hans Netterling. Data analysis: Johan Svensson, Johan Styrke, Danna Asad, Firas Aljabery. Manuscript writing/editing: Amir Sherif, Danna Asad, Johan Styrke, Firas Aljabery, Mohammad Hagsheno, Markus Johansson, Ylva Huge, Hans Netterling, Johan Svensson, Funding: Amir Sherif. Supervision: Amir Sherif, Firas Aljabery, Johan Styrke.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

On reasonable request, the corresponding author can make available all codified data from the data base used for this study.

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