

Do preoperative leukocyte and neutrophil levels have a predictive value on the complications of hypospadias repair in children?

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Summary

Objective: Surgeons observed that the outcomes after the same repair technique in the

same type of hypospadias performed by the same surgeon may be different. There may be some indeterminate factors that influence the results such as subclinical inflammation. Our study evaluated the predictor values of inflammatory hematologic parameters on the complications after hypospadias repair.

Materials and methods: We retrospectively reviewed the data of patients who underwent hypospadias repair between January 2016 and January 2019 in our clinic. Age at surgery, hypospadias type, repair technique, complications were recorded.

Patients who underwent Snodgrass repair by a single surgeon were included in the study while patients who underwent different techniques or procedures that were performed by other surgeons were excluded. The levels of white blood cell, neutrophil, lymphocyte, platelet and monocyte, the mean platelet volumes were recorded from blood test that were performed one day before surgery. Neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and other parameters were analyzed to determine their relationship with complications after hypospadias surgery.

Results: WBC and neutrophil levels were statistically higher in patients with complications ($p = 0.006$ and 0.017 respectively). Other hematological parameters were not different between patients with or without complications. To predict the complications, the WBC cutoff was $9500/\text{mm}^3$, the neutrophil cutoff was $3000/\text{mm}^3$.

Conclusions: WBC and neutrophil values were statistically significant in predicting the complications after Snodgrass repair in patients with hypospadias. Our result determined no relation between complications and NLR, PLR.

KEY WORDS: Hypospadias; Leukocyte; Neutrophil; NLR; Complication.

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INTRODUCTION

Hypospadias repair is one of the most common surgery in pediatric urology. More than 100 different procedures were described to obtain better results, but complication rates are still a challenge for the surgeons. However bet-

ter techniques and thinner suture materials reduce the rate of complications (1). Better wound dress materials and surgery with or without stent were also discussed to improve the results. Seniors had experienced that patients with same characteristics, operated with the same technique and material by the same surgeon had different results. The difference may be depending on subclinical inflammation that may be a predictor about these unexpected complications.

The neutrophils and the lymphocytes are the main cellular components of the immune system of human being. During an infection the level of white blood cells may vary depending on the stage of the disease, the patient's immunologic features and the etiology of the infection. Increment in the level of neutrophils and reduction in the level of lymphocytes shows a possible infection (2). All these parameters can be measured in complete blood count (CBC).

Physiological immune response of circulating white blood to various stressful events such as tissue injury, severe trauma characterized by major surgery, burns, sepsis syndrome consists in elevation of neutrophils and decrease of lymphocyte counts. This inflammatory response sometimes causes fibrosis and poor neovascularization which are the main factors for poor wound healing (3). It is shown that spongiobrosis with urethral stricture was related with inflammation (4, 5). Several medications with anti-inflammatory effect have been used to treat urethral strictures either systematically or locally (6-10). In adult's series, it was reported that neutrophil-lymphocyte ratio (NLR) revealed the inflammatory status of the urethral tissue predicting urethral stricture after non-hypospadias surgery (11). Also, NLR was shown as a marker to predict for systemic inflammatory response syndrome after flexible ureteroscopic lithotripsy (12). Subclinical systemic inflammation may have impact on the outcomes of hypospadias repair in children.

Preoperatively the number of white blood cell (WBC) and neutrophils, NLR, platelet-lymphocyte ratio (PLR) or mean platelet volume (MPV) may predict complications after hypospadias surgery, but this was not studied yet. The

aim of the present study is to investigate the relationship between the hematologic parameters and the complications after hypospadias repair in children.

MATERIALS AND METHODS

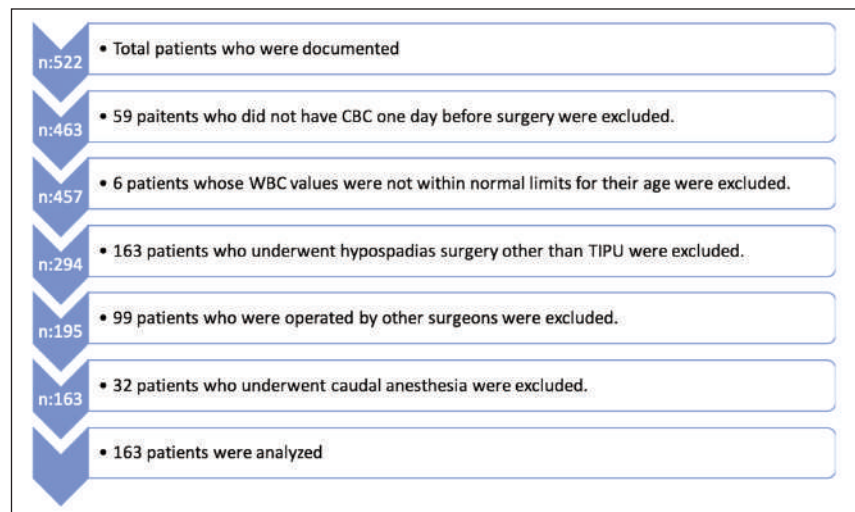
Institutional Review Board approval was obtained before chart review and data analysis with the reference number of 09.2020.1155. Informed consent was approved by the parents of all patients. Records of the children who underwent hypospadias repair between January 2015 and January 2019 in our clinic were reviewed. Data collected included age of the patients, types of hypospadias, repair techniques, suture materials, surgeons who performed the hypospadias repair, follow-up time, complications, and hematological parameters. Hematological parameters including white blood count (WBC), neutrophil, lymphocyte, monocytes, platelet counts, and mean platelet volume were recorded from the complete blood count (CBC) which was performed the day before surgery. Patients with hypospadias who underwent tubularized incised plate urethroplasty (TIPU) repair by a single surgeon (HT) were included. Patients with abnormal WBC values for their age in the complete blood count the day before the operation were excluded. Patients with follow up time shorter than 12 months and incomplete data were not recorded.

In the study period 522 patients who underwent hypospadias repair were recorded. 59 patients whose complete blood count was not performed the day before the surgery, 6 patients whose WBC values were not within the normal range for their age, 163 patients who underwent two-session hypospadias repair or who underwent hypospadias repair with another technique, 99 patients who were operated by other surgeons, and 32 patients who underwent caudal anesthesia, whose effect on the outcomes after hypospadias repair is controversial, were excluded from the study (Figure 1). Patients were divided into two groups depending on the presence of complication. Hematological parameters detected from CBC were statistically analyzed whether if they are related with complications or not.

Operative technique

All procedures were performed under general anesthesia and penile block was performed at the beginning of the procedure. Sterile urine was controlled with urine culture 3-7 days before the surgery. Antibiotic prophylaxis was applied one-hour prior the

Figure 1.
Flowchart.



surgery. All patients underwent TIPU technique by the same surgeon (HT). The urethral plate was tabularized over a 6 Fr urethral catheter in two layers, the first layer with continuous subcuticular 7/0 coated polyglactin sutures and the second layer with interrupted 7/0 coated polyglactin sutures. Tourniquet for less than 15 minutes was used while the dissection of glandular wings. A pedicle flap from dartos fascia was prepared and placed on the neourethra. Glanduloplasty was done with 6/0 polydioxanone sutures. Subcutaneous epinephrine was not used during surgery. The 6 Fr urethral catheter was left in place for seven days postoperatively. The patients were followed up in the second week, first month and third month postoperatively. Follow-up continues with outpatient visits every 3 months in the first year and once a year thereafter. Patients were evaluated for penile cosmetics, meatal and urethral steno-

Table 1.
Demographic features and hematological parameters of patients in the groups.

	Complication (-)			Complications (+)			P
	Mean ± sd/n-%	Median		Mean ± sd/n-%	Median		
Age at surgery (months)	43.5 ± 32.9	33.5		45.5 ± 38.4	29.0		0.874 ^m
Type of the hypospadias							
Distal	101	80.2%		21	56.8%		0.008 ^{x²}
Midpenile	22	17.5%		12	32.4%		0.082 ^{x²}
Proximal	3	2.4%		4	10.8%		0.078 ^{x²}
WBC (x10 ³)	8.8 ± 2.5	8.5		10.2 ± 3.0	9.7		0.006 ^m
Neutrophil	3356 ± 1563	3000		4176 ± 2054	3700		0.017 ^m
Lymphocyte	4302 ± 1726	4100		4630 ± 2372	4300		0.529 ^m
Monocyte	808 ± 462	700		803 ± 246	700		0.303 ^m
HB	12.0 ± 1.1	11.9		12.0 ± 1.1	11.9		0.810 ^m
PLT (x10 ³)	316.0 ± 83.4	313.5		325.5 ± 86.1	313.0		0.563 ^m
NLR	0.9 ± 0.5	0.8		1.4 ± 1.6	0.9		0.240 ^m
PLR	83.6 ± 34.7	80.2		102.7 ± 116.9	85.9		0.876 ^m
MLR	0.2 ± 0.2	0.2		0.2 ± 0.2	0.2		0.768 ^m
MPV	7.7 ± 0.8	7.6		7.8 ± 0.8	7.7		0.504 ^m

^mMann-Whitney U test. ^{x²} Chi-square test.

WBC: White blood cell; HB: Hemoglobin; PLT: Platelet; NLR: Neutrophil-Lymphocyte Ratio; PLR: Platelet-Lymphocyte Ratio; MLR: Monocyte-Lymphocyte Ratio; MPV: Mean Platelet Volume.

sis, urethrocutaneous fistula and for other complications with physical examination, calibration of the neourethra with 6-8 Fr catheter and voiding video.

Statistical analysis

In the descriptive statistics of the data, mean, standard deviation, median, minimum, maximum, frequency and ratio values were used. The distribution of variables was measured with the Kolmogorov-Smirnov test. The Mann-Whitney U test was used in the analysis of quantitative independent data. Chi-square test was used in the analysis of qualitative independent data, and Fisher-Exact test was used when the Chi-square test conditions were not met. ROC curve was performed to analyze the capacity of hematological parameters in predicting the complication of hypospadias repair. Probability chart was performed to determine the possibility of complications after surgery. Cut off values were determined according to Youden index. SPSS 27.0 program was used in the analysis. All p-values less than 0.05 were considered statistically significant.

RESULTS

One hundred sixty-three patients were analyzed retrospectively. The median age of the patients was 32 months (Table 1). Of the patients, 122 had distal hypospadias, 34 had midpenile hypospadias, and 7 had proximal hypospadias. There were 126 patients without complication and 37 with complications. The complications were urethral fistula in 19 patients, urethral stricture requiring reoperation in 3 patients, urethral diverticula in 3 patients, dehiscence (partial or complete) in 4 patients and mild meatal stenosis that solved with dilatation in 8 patients. Patients were divided into two groups according to the presence of complications and there was no difference between groups in case of age at operation ($p > 0.05$) (Table 1). The ratio of complications in patients with distal hypospadias was lower than the ratio of complications in patients with mid-penile and proximal hypospadias ($p = 0.008$). WBC and neutrophil levels were statistically higher in patients with complications ($p < 0.05$) (Table 1, Figure 2). NLR, PLR and other hematological parameters were not different between patients with or without complications (Table 1). Although *area under curve* (AUC) was not so high, significant effectiveness of WBC value was observed in predicting patients with and without complications (Table 2). WBC value was found to be a significant variable in the occurrence of complications. The cut off value of WBC to predict the complications was 9500 m/mm^3 , the sensitivity was 56.8%, specificity was 70.6%, (Figure 3), positive prediction was 36.2%, and negative prediction was 84.8%.

Figure 2.
WBC: White blood cell.

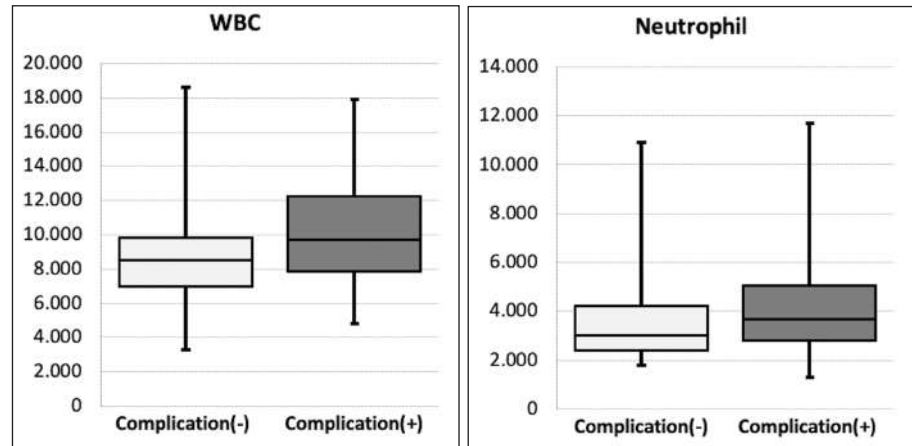


Table 2.
Area under curve for WBC and neutrophil values.

	AUC	95% CI	p
WBC	0.647	0.544 - 0.751	0.006
Neutrophil	0.629	0.527 - 0.731	0.017

WBC: White blood cell; AUC: Area under curve.

In predicting the patients with and without complications, the neutrophil count was also statistically significant (Table 2). The neutrophils cut off value to predict the complications was 3000 m/mm^3 , the sensitivity was 70.3%, specificity was 51.6% (Figure 3), positive prediction was 29.9%, and negative prediction was 85.5%. There was no statistically significant difference in NLR, PLR, MPV and also WBC and neutrophils between patients with or without urethral fistula ($p > 0.05$).

Figure 3.
Graphics of sensitivity and specificity of WBC and neutrophil values.

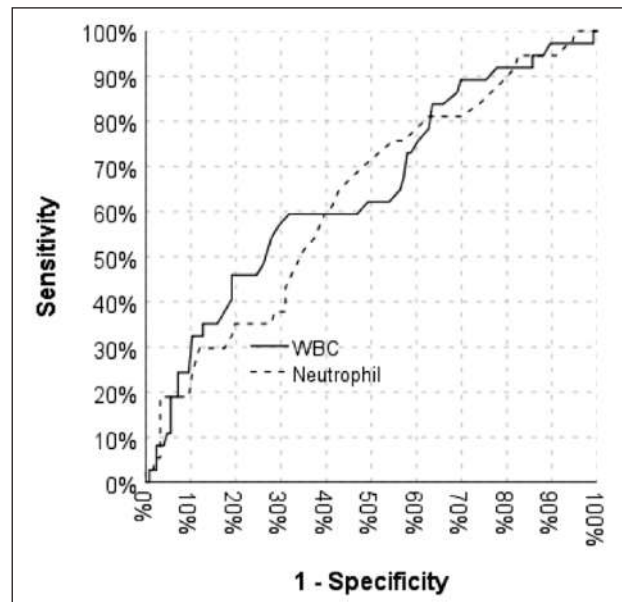
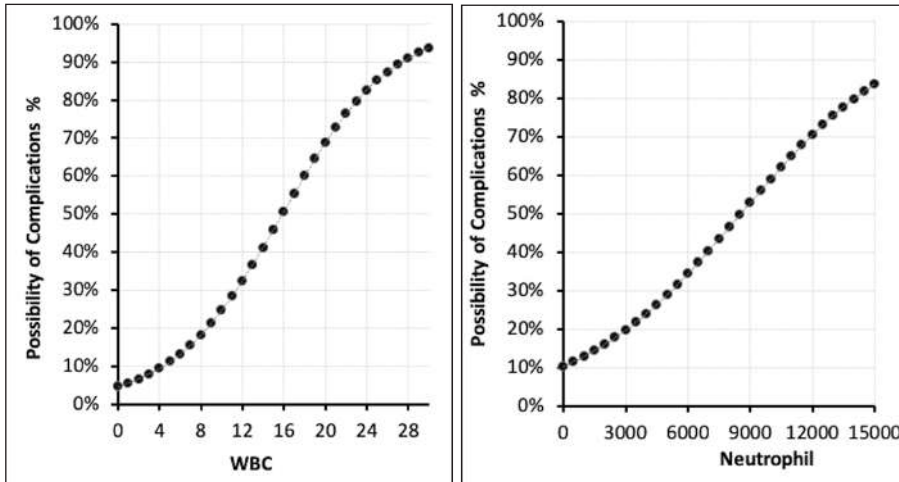


Figure 4.

Possibility graphics for WBC and neutrophil values.



DISCUSSION

Complications of hypospadias repair are reported frequently in the previous literature (1, 13). Especially the complications of the TIPU which is a commonly used technique are well known by pediatric urologists.

The main complications of this technique are urethral stricture, meatal stricture, urethral fistula, and dehiscence (14). To reduce the complication rate, surgeons used better suture materials, preferred waterproof and tension free suture lines, using dartos flap on the neourethra, etc. (15). But it is observed that results were different in patients with the same hypospadias type who underwent exactly same repair technique with using high-quality suture materials by same experienced surgeon.

The reasons of this difference are not clear yet. Subclinical inflammation may be a factor for complications of hypospadias surgery and our study revealed that WBC or neutrophil value could be predictors for these complications. WBC differs in the systemic inflammation. This inflammatory response sometimes causes fibrosis and poor neovascularization which are the main factors for poor wound healing (3). *Hampson et al.* reported subepithelial inflammation results with spongiositis (5). *Mundy* reported a review article in 2011 and determined that 40% of urethral strictures were related with inflammation (4). *Sciarra et al.* (6) used anti-inflammatory drugs to reduce urethral complications after TURP. Based on the same mechanism, several medications including colchicine (16), mitomycin-c (7), triamcinolone (8), and corticosteroids (9), which all have anti-inflammatory effects, have been used to treat urethral strictures either systematically or locally. Therefore, subclinical systemic inflammation may have impact on the outcomes of hypospadias repair. Level of leukocyte and neutrophils, *Neutrophil-to-Lymphocyte Ratio* (NLR), *Platelet-to-Lymphocyte Ratio* (PLR) and *Mean Platelet Volume* (MPV) are simple markers that can reflect the inflammation which can easily be obtained from CBC (18-21).

This study evaluated the predictive values of the WBC, neutrophils, NLR, PLR and MPV on the results of hypospadias repair. The best of our knowledge, this study is the first study that evaluate the value or capacity of hematological parameters in predicting the complications

of hypospadias repair in children. There are three studies that evaluated the impact of these parameters in recurrence of urethral stricture after surgical treatment in adults (10, 11, 22). *Topaktas et al.* (22) had reported 117 adult cases with urethral stricture who underwent urethroplasty and assessed the correlation between the systemic inflammation markers and recurrence rate of urethral stricture after surgery. They determined that neutrophil, lymphocyte counts, or their ratio are not the predictors for recurrence urethral stricture after urethroplasty.

Urkmez et al. (11) reported a study to determine the impact of these parameters in predicting the course of the urethral stricture and its recurrence in adults and they emphasized that by using NLR, inflammatory status of the urethral tissue can be revealed, and possible urethral stricture recurrence can be predicted. *Gül et al.* (10) reported the value of hematologic parameters in predicting urethral stricture after transurethral resection of prostate and determined that PLR can be used to predict the urethral stricture. Our results revealed that WBC value and neutrophil counts are related with complications after hypospadias repair (Figure 4). However, other parameters such as NLR, PLR, MLR, and MPV were not indicative of postoperative complications.

Urkmez et al. (11) reported that the cut-off value of NLR in detecting the recurrence after internal urethrotomy was 2.25 with a sensitivity of 70% and specificity of 67.7%. Our study revealed that the cut off value of WBC to predict the complications was 9500 m/mm^3 (AUC: 0.647, $p = 0.006$), the sensitivity was 56.8%, positive prediction was 36.2%, specificity was 70.6%, and negative prediction was 84.8%. The neutrophil's cut off value to predict the complications was 3000 m/mm^3 (AUC: 0.629, $p = 0.017$), the sensitivity was 70.3%, positive prediction was 29.9%, specificity was 51.6%, and negative prediction was 85.5%. The major limitation of our study is its retrospective design. We did not analyze the penile lengths of the patients such as glans diameter, width of the plate and depth of the groove. Although some studies suggested that these measurements have impact on the outcomes of the hypospadias repair (23-25), *Bush and Snodgrass* argue that there is no effect of these factors on postoperative complications (26). Single surgeon and single operative technique with exactly the same details such as penile block and tourniquet use, also not using caudal block and local epinephrine are the superiority of our study. The considerable number of patients of this study is another superiority.

CONCLUSIONS

WBC and neutrophil values were higher in pediatric patients with complications who underwent TIPU repair by single surgeon. Other hematological parameters such

as NLR, PLR, MLR were not related with complications after hypospadias repair. Our results revealed that postponing the hypospadias surgery may be more appropriate in patients with high blood WBC and neutrophil values.

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