Results

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Demographic and clinical characteristics:

This study was carried out on 75 patients admitted in the urology department in Benha University Hospital together with 15 apparently healthy control subjects: -

Group I:

Included 60 patients with newly diagnosed squamous cell carcinoma of the bladder who were diagnosed by histopathology following cystoscopic biopsy of the tumor. They were 49 males (81.67%) and 11 females (18.33%) with age ranging from 39 – 82 years with a mean of 63.38 ± 10.43.

Group II:

Included 15 patients with other benign urological conditions (5 cases of urinary tract infection, 3 cases of benign prostatic hyperplasia, 3 cases of stone bladder, 2 cases of stone ureter, one case of stress urinary incontinence and one case of impotence). They were 9 males (60%) and 6 females (40%) with age ranging from 38 – 72 years with a mean of 61.26 ± 8.89.

Group III:

Included 15 apparently healthy individuals matched in age and sex with the patients groups and they were clinically free from any urological disease. They were 9 males (60%) and 6 females (40%) with age ranging from 39 – 74 years with a mean of 60.33 ± 9.55.

Table (3) Age of patients among the groups under the study.

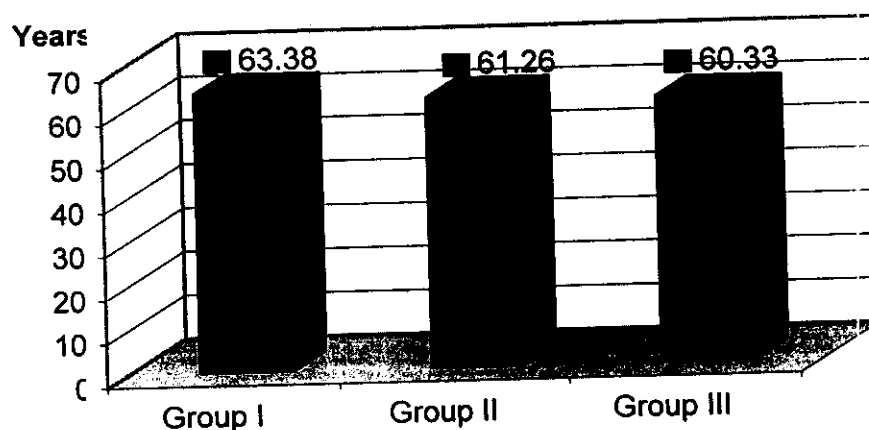| Group	Range (years)	Mean ± SD
Group I (n = 60)	39 – 82	63.38 ± 10.43
Group II (n = 15)	38 – 72	61.26 ± 8.89
Group III (n = 15)	39 – 74	60.33 ± 9.55

Fig. (1): Mean age of patients in the groups under study.

Table (4): Comparison of ages between the different studied groups.

Group	Z value	P value
Group I & group II	1.216	>0.05*
Group I & group III	1.369	>0.05*
Group II & group III	1.112	>0.05*

*No significant difference was encountered in age between each two of the 3 groups.

Table (5): Comparison of ages between the different grades of the tumors in the studied group I.

Item	Grade I (n = 28)	Grade II (n = 18)	Grade III (n = 14)	P value
Mean ± SD	61.82 ± 9.83	66.61 ± 9.82	62.35 ± 12.08	>0.05*

*No significant difference was encountered in age between the different grades of the tumors in the studied group I.

Table (6): Comparison of ages between the superficial and invasive stages of the tumors in the studied group I.

Item	Superficial stages (n = 36)	Invasive stages (n = 24)	P value
Mean ± SD	64.13 ± 9.89	62.25 ± 11.3	>0.05*

*No significant difference was encountered in age between the superficial and invasive stages of the tumors in the studied group I.
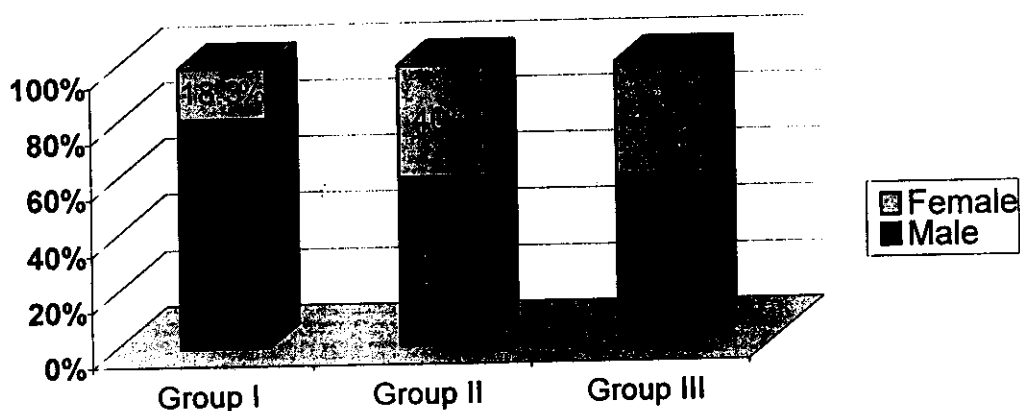

Fig. (2): Sex distribution among studied groups.

Table (7): Urinary creatinine of patients among the studied groups.

Group	Range (mg/dl)	Mean ± SD
Group I	78 – 174	115.05 ± 21.5
Group II	98 – 168	121.46 ± 20.18
Group III	98 – 142	131.86 ± 13.6

Table (8): Comparison of urinary creatinine between the different studied groups.

Group	Z value	P value
Group I & group II	-1.119	>0.05*
Group I & group III	-3.331	<0.001**
Group II & group III	-1.659	<0.05***

*No significant difference was encountered in urinary creatinine between group I and group II.

**High significant decrease was encountered in urinary creatinine in group I when compared to group III.

***Significant decrease was encountered in urinary creatinine in group II when compared to group III.

The descriptive statistics of NMP22, urinary bladder cancer antigen (UBC) with and without correction by urinary creatinine (expressed by the median, the range, the mean and SD) and urine RBCs among the studied groups are presented in **Tables (9, 13, 15) and Figures (3, 4, 5, 6, 7).**

Table (9): Descriptive statistics of NMP22, UBC (both with and without correction by urinary creatinine) and urine RBCs among studied groups.

Variant		GROUP I NO.=60	GROUP II NO.=15	GROUP III NO.=15
NMP22 U/ml	Median	120.9	4.8	2.4
	Range	2.1-196.9	1.4-60	0.7-24
	Mean	103.2	11.9	4
	SD	69.9	16	5.7
NMP22 U/mg. creatinine	Median	123.7	3.2	1.8
	Range	1.5-193.3	1.0-52.6	0.5-16.6
	Mean	94.1	9.6	2.9
	SD	65.8	14.	3.9
UBC µg/l	Median	120.2	3.2	2.5
	Range	3.5-194.2	2.3-50.8	0.8-17
	Mean	104.9	10.2	3.5
	SD	60.6	15.3	3.9
UBC µg/gm. creatinine	Median	105.4	2.3	2
	Range	2.8-220.6	0.6-36.3	0.6-10.7
	Mean	95.2	7.2	2.6
	SD	60.3	10.3	2.5
Urine RBCs	10 RBC/µl OR more	65%	40%	0%

Table (10): Comparison of NMP22 and UBC (with and without correction by urinary creatinine) between group I and group II.

Variant	Group I Mean ± SD	Group II Mean ± SD	P value
NMP22 U/ml	103.2 ± 69.9	11.9 ± 16	<0.001*
NMP22 U/mg. creatinine	94.1 ± 65.8	9.6 ± 14	<0.001*
UBC µg/l	104.9 ± 60.6	10.2 ± 15.3	<0.001*
UBC µg/gm. creatinine	95.2 ± 60.3	7.2 ± 10.3	<0.001*

*High significant increase was encountered in both NMP22 & UBC (with and without correction) in group I when compared to group II.

Table (11): Comparison of NMP22 and UBC (with and without correction by urinary creatinine) between group I and group III.

Variant	Group I Mean ± SD	Group III Mean ± SD	P value
NMP22 U/ml	103.2 ± 69.9	4 ± 5.7	<0.001*
NMP22 U/mg. creatinine	94.1 ± 65.8	2.9 ± 3.9	<0.001*
UBC µg/l	104.9 ± 60.6	3.5 ± 3.9	<0.001*
UBC µg/gm. creatinine	95.2 ± 60.3	2.6 ± 2.5	<0.001*

*High significant increase was encountered in both NMP22 & UBC (with and without correction) in group I when compared to group III.

Table (12): Comparison of NMP22 and UBC (with and without correction by urinary creatinine) between group II and group III.

Variant	Group II Mean ± SD	Group III Mean ± SD	P value
NMP22 U/ml	11.9 ± 16	4 ± 5.7	<0.05*
NMP22 U/mg. creatinine	9.6 ± 14	2.9 ± 3.9	<0.05*
UBC µg/l	10.2 ± 15.3	3.5 ± 3.9	<0.05*
UBC µg/gm. creatinine	7.2 ± 10.3	2.6 ± 2.5	>0.05**

*Significant increase was encountered in NMP22 (with and without correction) and UBC (without correction) in group II when compared to group III.

**No significant difference was encountered in UBC (after correction) between group II & group III.
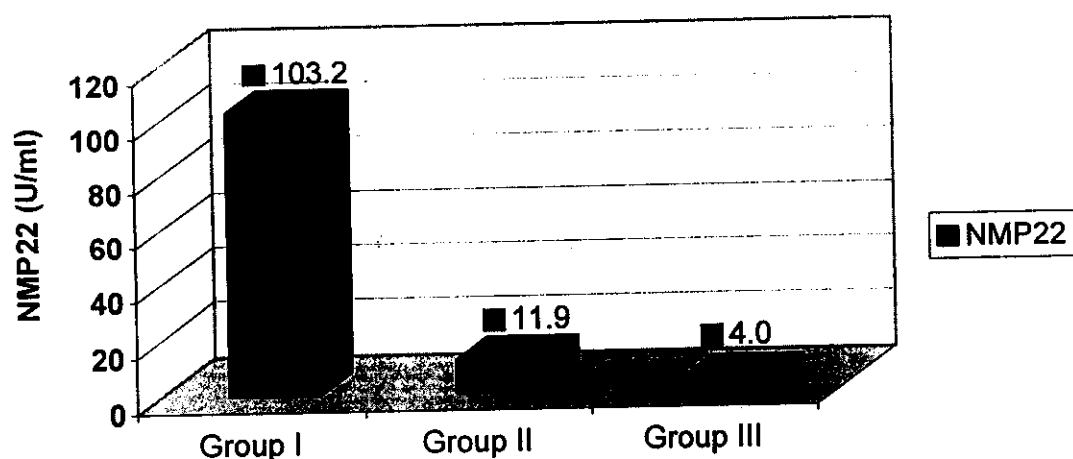

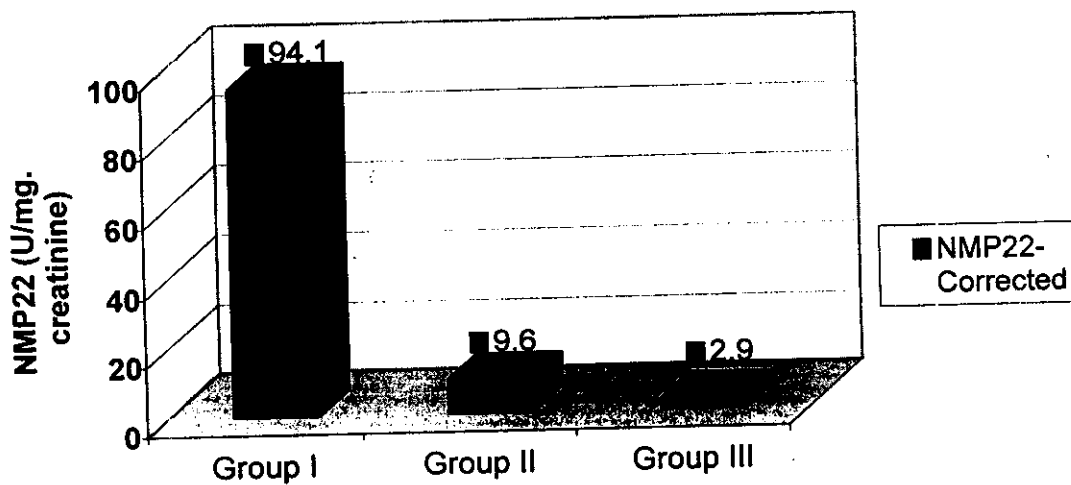Fig. (3): NMP22 mean values among the studied groups.

Fig. (4): NMP22 mean values after correction with urinary creatinine among the studied groups.
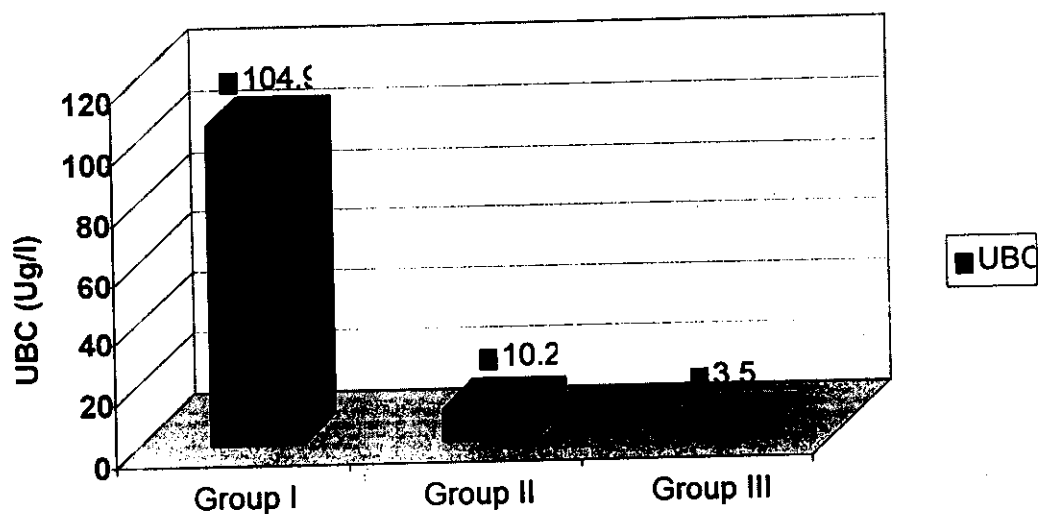

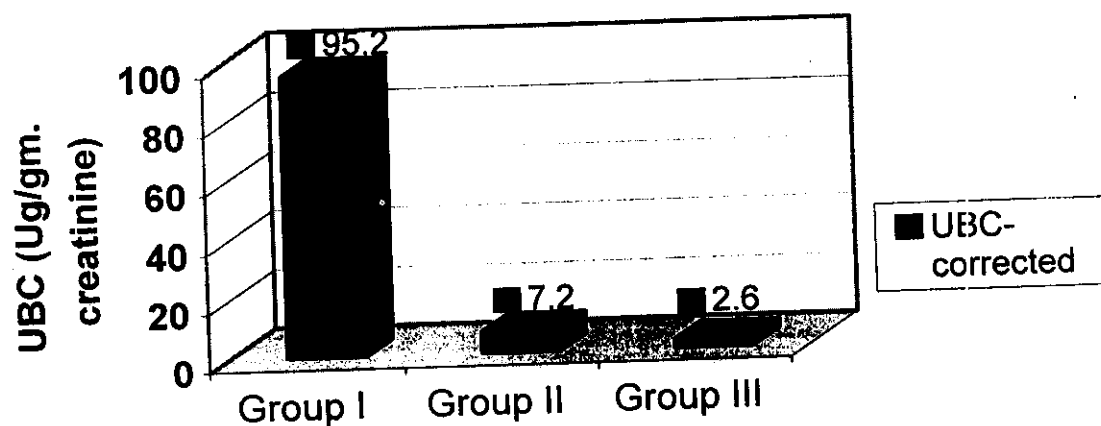**Fig. (5): UBC mean values among the studied groups.**

Fig. (6): UBC mean values after correction with urinary creatinine among the studied groups.
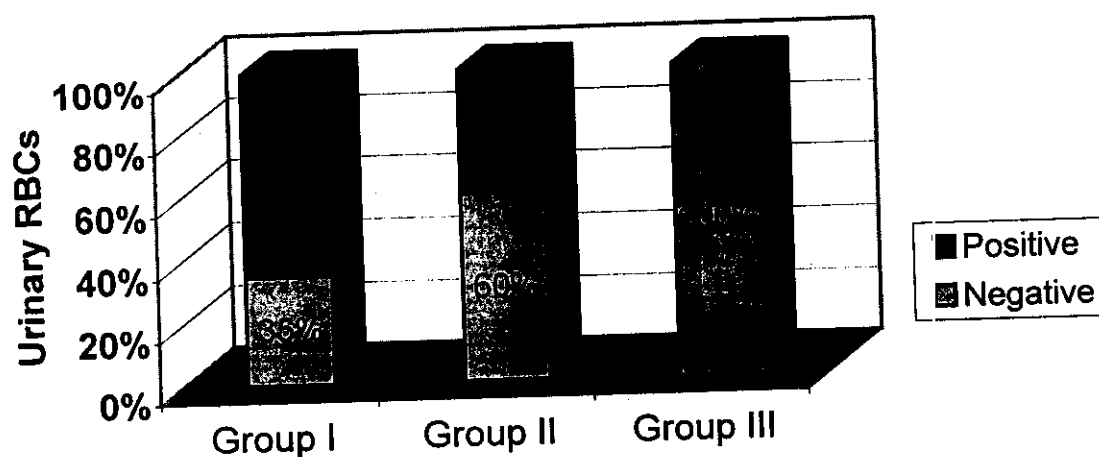
Fig. (7): Urine erythrocyte distribution among studied groups.

Table (13): Descriptive statistics of NMP22 and UBC (with and without correction) among different grades of the tumors in the studied group I.

VARIANT		GRADE I NO.=28	GRADE II NO.=18	GRADE III NO.=14
NMP22 U/ml	Median	131	116.5	128.35
	Range	2.6-196.9	2.1-186.4	2.5-192.4
	Mean	103.49	95.88	112.1
	SD	74.39	69.49	64.96
NMP22 U/mg. creatinine	Median	123	124.6	125.6
	Range	2.9-181.5	1.7-193.3	1.5-182
	Mean	90.7	93.87	101.31
	SD	64.86	70.75	65.64
UBC µg/l	Median	119.3	124.2	119.8
	Range	4.0-194.2	3.5-184.6	4.0-154
	Mean	101.97	108.07	106.72
	SD	67.03	61.31	49.15
UBC µg/gm. creatinine	Median	103.1	119.75	95.45
	Range	4.1-220.6	3.3-213.8	2.8-168
	Mean	91.5	103.35	92.16
	SD	65.3	63.24	47.78

Table (14): Comparison of NMP22 & UBC (with and without correction by urinary creatinine) among different grades of the tumors in studied group I.

Item	Grade I Mean ± SD	Grade II Mean ± SD	Grade III Mean ± SD	P value
NMP22 U/ml	103.49 ± 74.39	95.88 ± 69.49	112.1 ± 64.96	>0.05*
NMP22 U/mg. creatinine	90.7 ± 64.8	93.87 ± 70.75	101.31 ± 65.64	>0.05*
UBC µg/l	101.97 ± 67.03	108.07 ± 61.31	106.72 ± 49.15	>0.05*
UBC µg/gm. creatinine	91.5 ± 65.3	103.35 ± 63.24	92.16 ± 47.78	>0.05*

*No significant difference was encountered in NMP22 & UBC (with and without correction) between the different grades of the tumors in studied group I.

Table (15): Descriptive statistics of NMP22 and UBC (with and without correction by urinary creatinine) among superficial & invasive stages of the tumors in the studied group I.

| VARIANT		SUPERFICIAL NO.=36	INVASIVE NO.=24
NMP22 U/ml	Median	120.4	141.4
	Range	2.1-196.9	2.5-192.4
	Mean	94.05	116.96
	SD	72.29	65.27
NMP22 U/mg. creatinine	Median	117.9	127.75
	Range	1.7-193.3	1.5-182
	Mean	86.66	105.32
	SD	68.12	61.88
UBC μg/l	Median	117.25	121.6
	Range	3.5-192.6	6.2-194.2
	Mean	99.26	113.38
	SD	64.42	54.77
UBC μg/gm. creatinine	Median	102.2	112.25
	Range	2.8-213.8	5.0-220.6
	Mean	89.19	104.38
	SD	60.73	59.7

Table (16): Comparison of NMP22 & UBC (with and without correction by urinary creatinine) among superficial & invasive stages of the tumors in the studied group I.

Variant	Superficial Mean ± SD	Invasive Mean ± SD	P value
NMP22 U/ml	94.05 ± 72.29	116.96 ± 65.27	>0.05*
NMP22 U/mg. creatinine	86.66 ± 68.12	105.32 ± 61.88	>0.05*
UBC µg/l	99.26 ± 64.42	113.38 ± 54.77	>0.05*
UBC µg/gm. creatinine	89.19 ± 60.73	104.38 ± 59.7	>0.05*

*No significant difference was encountered in NMP22 & UBC (both with and without correction) between superficial and invasive stages of the tumors in studied group I.

By using the **Receiver Operator Characteristic curve (ROC curve)** it was found that:

- At a cutoff value of 7.0 U/ml for NMP22, maximum sensitivity (**76.67%**) and specificity (**80%**) was observed differentiating between cases of squamous cell carcinoma of the bladder (**group I**) and other non malignant cases (**group II & group III**).

- At a cutoff value of 7.5 µg/l for UBC, maximum sensitivity (**85%**) and specificity (**86.67%**) was observed differentiating between cases of squamous cell carcinoma of the bladder (**group I**) and other non malignant cases (**group II & group III**).
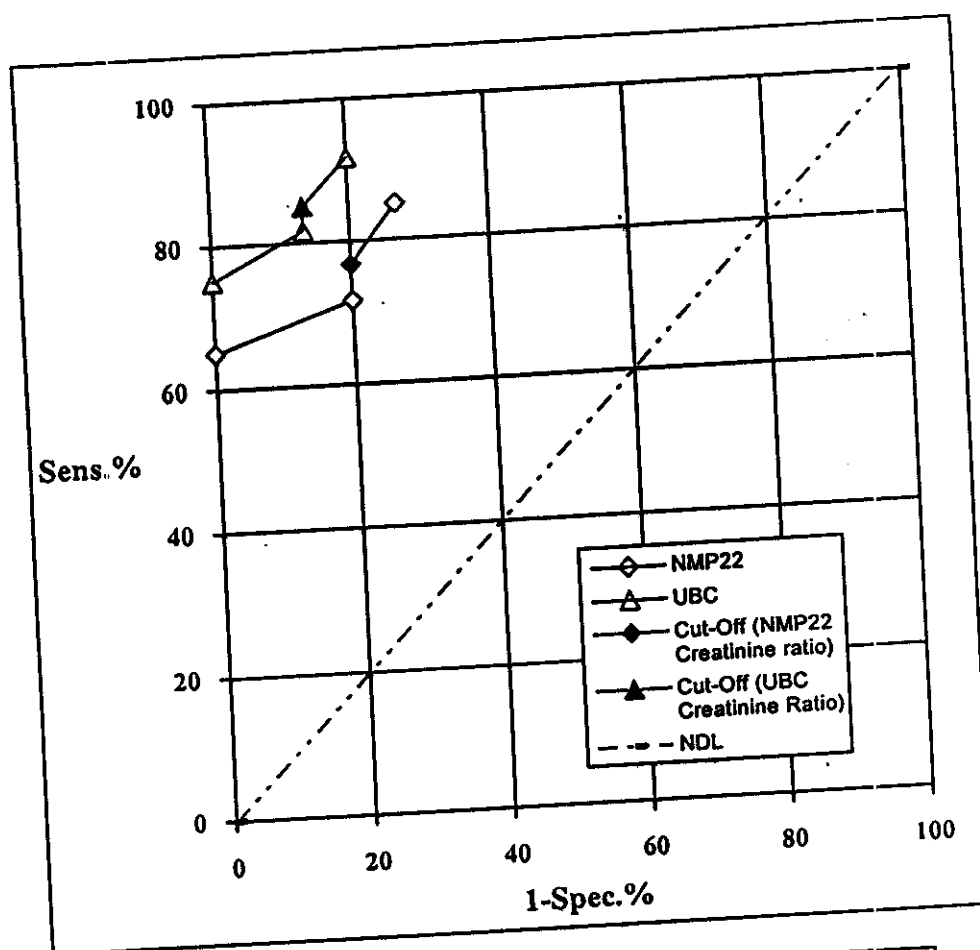
Fig. (8): ROC curve for NMP22 and UBC for all subjects under the study with best cutoff values of 7.0 U/ml for NMP22 and 7.5 µg/l for UBC.

- At a cutoff value of 5 U/mg. creatinine for corrected NMP22, maximum sensitivity **(83.33%)** and specificity **(83.33%)** was observed differentiating between cases of squamous cell carcinoma of the bladder **(group I)** and other non malignant cases **(group II & group III)**.

- At a cutoff value of 6 μg/gm. creatinine for corrected UBC, maximum sensitivity **(85%)** and specificity **(86.67%)** was observed differentiating between cases of squamous cell carcinoma of the bladder **(group I)** and other non malignant cases **(group II & group III)**.
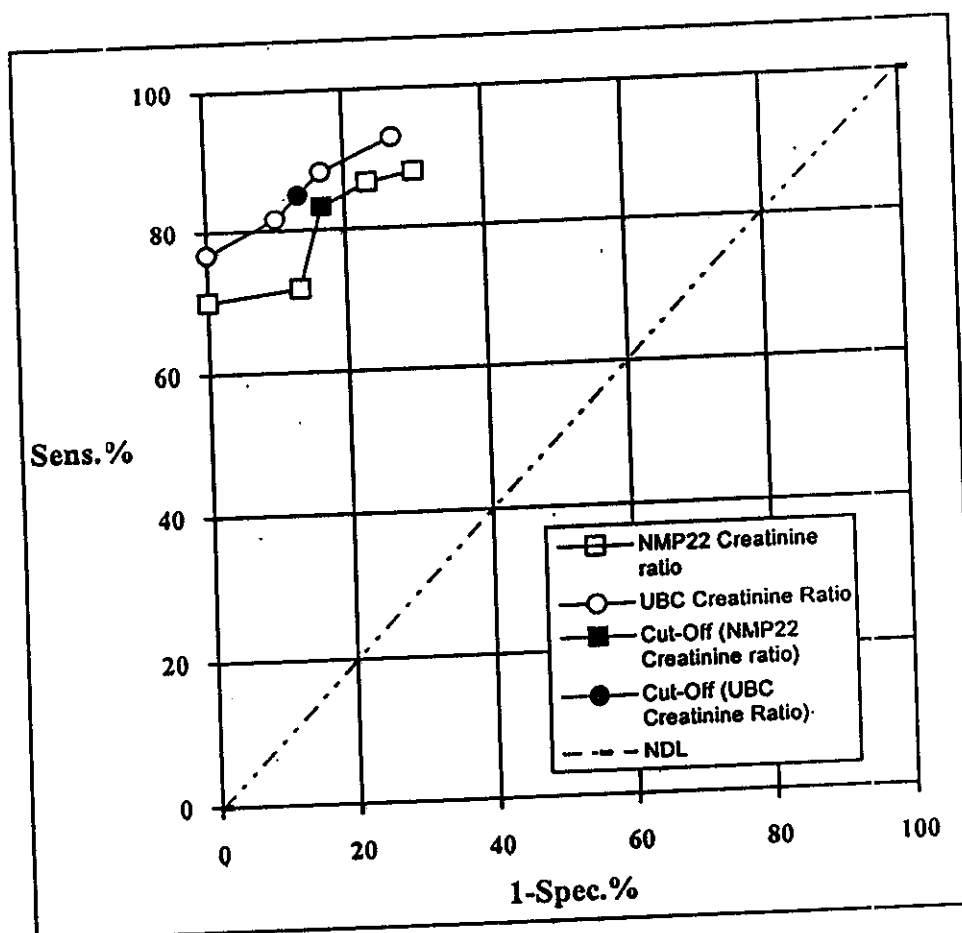
AUC	
NMP22 Creatinine Ratio	0.779
UBC Creatinine Ratio	0.829

Fig. (9): ROC curve for corrected NMP22 and UBC for all subjects under the study with best cutoff values of 5.0 U/mg. creatinine for corrected NMP22 and 6.0 µg/gm. creatinine for corrected UBC.

Table (17): Overall sensitivity, specificity, positive and negative predictive values together with total accuracy of NMP22 and UBC (with and without correction by urinary creatinine).

ITEM	Cutoff	Sensitivity %	Specificity %	+Ve P.V. %	-Ve P.V. %	Accuracy %
NMP22	7.0 U/ml	76.67	80	88.46	63.16	77.78
NMP22 / CREATININE	5.0 U/mg. creatinine	83.33	83.33	90.91	71.43	83.33
UBC	7.5 µg/l	85	86.67	92.73	74.29	85.56
UBC / CREATININE	6 µg/gm. creatinine	85	86.67	92.73	74.29	85.56

Table (18): Differential diagnostic properties of a combination of NMP22 and UBC (with and without correction by urinary creatinine).

ITEM	Sensitivity %	Specificity %	+Ve P.V. %	-Ve P.V. %	Accuracy %
NMP22 + UBC	88.3	86.7	92.9	78.8	87.8
NMP22 – C. + UBC – C.	95.0	83.3	91.9	89.3	91.1
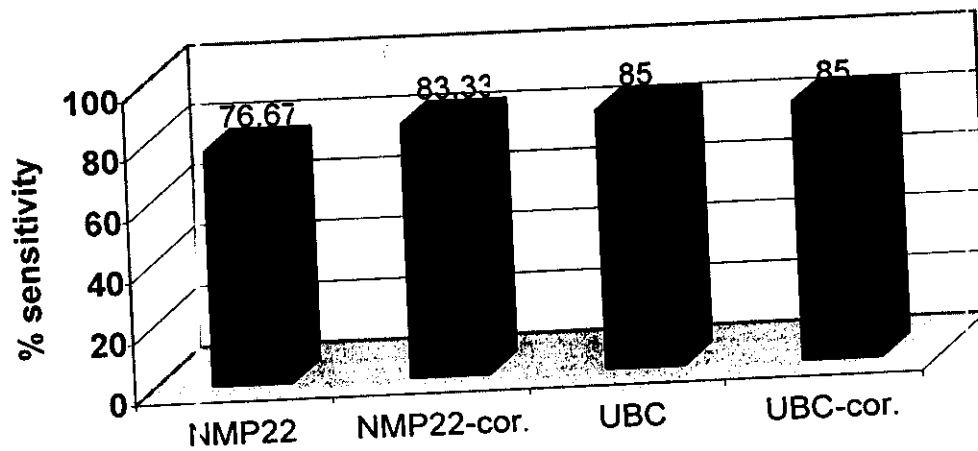
Fig. (10): Overall sensitivity of NMP22 and UBC (both with and without correction by urinary creatinine) in malignant cases.
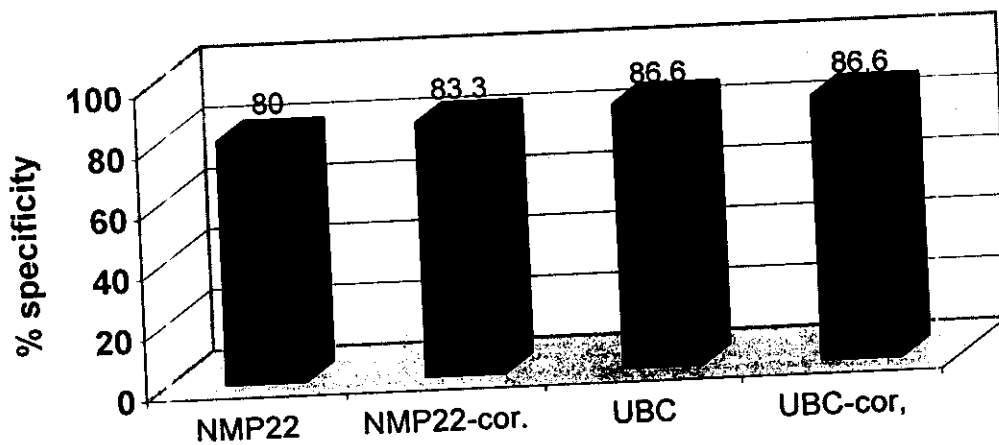
Fig. (11): Overall specificity of NMP22 and UBC (both with and without correction by urinary creatinine) in non-malignant cases.

Table (19): Correlation coefficient among age, urinary creatinine, NMP22, UBC, NMP22- C (corrected), UBC- C (corrected) and each other in studied group I.

	Age	U. Creat.	NMP22	UBC	NMP22- C	UBC- C
Age	1.0000					
U. Creat.	-0.5133	1.0000				
NMP22	0.2159	-0.0472	1.0000			
UBC	0.5225	-0.0860	0.3191	1.0000		
NMP22-C	-0.8282	0.1365	-0.1044	-0.1096	1.0000	
UBC- C	0.1378	-0.0099	0.0354	-0.0879	0.3726	1.0000

Critical Value (1 – Tail, 0.05) = + or – 0.21453.

Table (20): Correlation coefficient among age, urinary creatinine, NMP22, UBC, NMP22- C (corrected), UBC- C (corrected) and each other in studied group II.

	Age	U. Creat.	NMP22	UBC	NMP22- C	UBC- C
Age	1.0000					
U. Creat.	-0.4575	1.0000				
NMP22	0.1584	0.1918	1.0000			
UBC	-0.0620	-0.0573	0.3369	1.0000		
NMP22-C	-0.2541	0.1032	0.0008	-0.3541	1.0000	
UBC- C	0.0793	-0.1122	-0.0267	-0.0586	0.4202	1.0000

Critical Value (1 – Tail, 0.05) = + or – 0.44218.

Table (21): Correlation coefficient among age, urinary creatinine, NMP22, UBC, NMP22- C (corrected), UBC- C (corrected) and each other in studied group III.

	Age	U. Creat.	NMP22	UBC	NMP22- C	UBC- C
Age	1.0000					
U. Creat.	-0.1924	1.0000				
NMP22	-0.0491	-0.2298	1.0000			
UBC	-0.1212	0.0599	-0.0547	1.0000		
NMP22-C	0.0893	0.2692	-0.2612	-0.3037	1.0000	
UBC- C	0.3781	0.0645	-0.1277	-0.2428	0.7067	1.0000

Critical Value (1 – Tail, 0.05) = + or – 0.44218.

From the previous 3 tables we found that:

- There was positive significant correlation between NMP22 and UBC (both before and after correction by urinary creatinine) among patients in group I.

- There was positive non-significant correlation between NMP22 and UBC (both before and after correction by urinary creatinine) among patients in group II.

- There was negative non-significant correlation between NMP22 and UBC (both before and after correction by urinary creatinine) among healthy subjects in group III.

Master sheet for the cases of squamous cell carcinoma of the bladder in group I.

#	Age (Y)	Sex	Grade	Stage	U. creat. mg/dl	NMP22 U/ml	NMP22-C. U/mg. creat.	UBC ug/l	UBC-C. ug/gm. creat.	Microsc. RBCs
1	82	Male	II	T1	121	168.6	139.3	116.3	96.1	100
2	59	Male	I	T2	88	2.6	2.9	194.2	220.6	2
3	72	Male	III	T1	140	98	70	140	100	30
4	55	Male	I	Ta	98	121.4	123.8	114.6	116.9	45
5	68	Female	I	T1	114	187	164	8.5	7.4	15
6	69	Female	I	T1	118	145.5	123.3	131.4	111.3	15
7	59	Male	II	T2	120	148.4	123.6	160	133.3	2
8	69	Male	III	T1	110	136.2	123.8	92.8	84.3	3
9	59	Male	I	Ta	128	8	6.2	6.5	5	2
10	70	Male	II	T2	91	114.3	125.6	146.6	161	100
11	50	Male	I	Ta	124	168.2	135.6	112	90.3	20
12	58	Male	II	T1	121	6	4.9	165.2	136.5	2
13	82	Male	I	T1	86	7	8.1	26.8	31.1	2
14	44	Female	III	T1	148	120.5	81.4	154.6	104.4	20
15	68	Female	III	T2	92	142.8	155.2	119.6	130	100
16	70	Female	III	T1	101	174.6	172.8	130.9	129.6	35
17	48	Male	III	T2	132	168.2	127.4	120	90.69	15
18	53	Male	III	T1	140	4.5	3.2	4	2.8	15
19	78	Male	II	Ta	101	144.6	143.1	120.4	119.2	100
20	54	Male	I	T3	117	168.7	144.1	44.3	37.8	15
21	64	Male	III	T2	92	117.9	128.1	154.6	168	15
22	64	Male	I	T2	124	3	2.4	6.2	5	2
23	74	Male	II	T1	98	149	152	136.9	139.6	4
24	66	Male	i	T2	142	188.4	132.6	120.4	84.7	15
25	68	Male	III	T1	130	167.6	128.9	108.6	83.5	4
26	41	Male	III	T2	168	2.5	1.5	84.3	50.1	3
27	75	Male	II	T1	78	116.8	149.7	166.8	213.8	100
28	78	Male	II	T3	102	148.3	145.3	172	168.6	25
29	58	Female	II	T1	114	78.8	69.1	184.6	161.9	100
30	54	Male	III	Ta	123	3.5	2.8	4.7	3.8	4

Master sheet for the cases of squamous cell carcinoma of the bladder in group I (cont.).

#	Age (Y)	Sex	Grade	Stage	U. creat. mg/dl	NMP22 U/ml	NMP22- C. U/mg. creat.	UBC ug/l	UBC- C. ug/gm. creat.	Microsc. RBCs
31	65	Male	II	T1	103	166.4	161.5	26.8	26	2
32	00	Male	?	T2	109	68.7	63	116.9	107.2	100
32	00	Male	?	T1	98	154.9	128	?	4.1	3
33	60	Male	I	T1	118	149.1	126.3	134.2	113.7	20
34	63	Male	I	T1	78	142	182	91.5	117.3	15
35	74	Female	III	T2	96	140.8	146.6	180.8	188.3	20
36	67	Male	I	T2	134	8	5.9	192.6	143.7	5
37	48	Male	I	T1	124	174.9	141	122.8	99	100
38	56	Male	I	T3	121	5	4.1	153.6	126.9	15
39	70	Male	I	T1	92	151.3	164.4	128	139.1	2
40	78	Male	II	T2	101	149	147.5	170.6	168.9	15
41	71	Male	I	T1	107	3	2.8	114	106.5	5
42	62	Male	II	T1	170	116.2	68.3	66.8	39.2	100
43	44	Male	II	T3	114	189.8	166.4	168.3	147.6	100
44	64	Male	I	T2	124	2.1	1.7	4.3	3.4	2
45	60	Female	II	Ta	117	186.4	159.3	140.8	120.3	100
46	64	Male	II	T2	98	120.3	122.7	24.8	25.3	15
47	74	Male	I	T1	104	6.6	6.3	3.5	3.3	2
48	66	Male	II	T1	110	66.9	60.8	118.2	107.4	100
49	68	Female	I	T1	136	114	83.8	78.9	58	20
50	53	Male	I	T3	108	6	5.5	8.4	7.7	15
51	70	Female	II	T2	88	140.6	159.7	176.3	200.3	3
52	71	Male	I	T1	106	192.4	181.5	150.6	142	25
53	68	Female	III	T3	99	13.2	13.3	84	84.8	100
54	58	Male	ii	T1	110	4	3.6	179.6	163.2	15
55	64	Male	I	T1	118	20.8	17.6	7	5.9	20
56	59	Male	I	T2	174	196.9	113.1	134.2	77.1	2
57	41	Male	I	T1	110	6	5.4	6.5	5.9	5
58	59	Male	I	T1	110	188.3	171.1	120.8	109.8	20
59	71	Male	I	T1	110	98.8	59.8	138	83.6	35
60	80	Male	III	T2	165					

Master sheet for other benign urological conditions (group II)

#	Age (Y)	Sex	Pathology	U. Creatin. mg/dl	NMP22 U/ml	NMP22- C. ug/mg Creat	UBC ug/l	UBC- C. ug/gm Creat	Microsc. RBCs	Microsc. Pus cells
1	54	Male	UTI	108	1.4	1.3	2.3	2.1	10	30
2	68	Male	UTI	114	60	52.6	41.4	36.3	3	25
3	60	Female	UTI	128	28.4	22.1	4.7	3.6	3	100
4	72	Male	UTI	98	4.8	4.9	1.9	1.9	2	20
5	38	Female	Stress urinary	140	2.5	1.8	3.2	2.3	15	4
6	69	Male	Stone ureter	116	4	3.4	2.4	2	15	2
7	52	Male	Impotence	168	1.8	1	3.1	1.8	2	1
8	66	Female	UTI	130	26.2	20.1	50.8	23.6	10	50
9	61	Female	Stone bladder	113	3.2	2.8	20.4	18	6	2
10	69	Male	BPH	98	5.5	1.9	2.8	0.6	10	3
11	54	Female	Stone bladder	125	4	3.2	7.1	5.7	3	20
12	62	Male	BPH	104	20.4	19.6	2.8	2.7	?	4
13	66	Male	BPH	145	4.8	3.3	3	2	1	2
14	68	Female	Stone bladder	98	3	3	4.4	4.5	6	1
15	60	Male	Stone ureter	136	4.1	3	3.2	2.3	20	

Master sheet for apparently healthy subjects (group III)

#	Age (Y)	Sex	U. Creatin. mg/dl	NMP22 U/ml	NMP22- C. ug/mg. creat.	UBC Ug/l	UBC- C. ug/gm. creat.	Microsc. RBCs	Microsc. Pus cells
1	67	Male	148	2.1	1.4	1.4	0.9	0	2
2	46	Male	136	1.3	0.9	1.6	1.1	1	1
3	57	Male	110	1.5	1.3	3.5	3.2	0	3
4	74	Male	130	0.7	0.5	2.1	1.6	2	4
5	71	Female	144	24	16.6	4.2	2.9	2	0
6	67	Female	135	3.4	2.5	1.8	1.3	0	2
7	59	Male	124	4.8	3.8	3.6	2.9	2	1
8	68	Female	138	6.8	4.9	2.8	2.0	0	2
9	62	Female	158	1.6	1.0	17	10.7	1	1
10	56	Male	129	2.5	1.9	0.8	0.6	2	2
11	69	Female	134	2.4	1.8	1.2	0.9	2	2
12	39	Male	112	3.3	2.9	4.6	4.1	4	3
13	56	Male	114	4.1	3.6	5.2	4.5	1	1
14	54	Male	142	0.8	0.5	1.0	0.7	0	2
15	60	Female	124	1.4	1.1	2.5	2.0	2	5