RESEARCH ARTICLE

New Immunological Markers of Thromboembolic and Hemorrhagic Complications after Coronary Artery Bypass Grafting

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Abstract

Aim and Scope: A total of 125 patients suffering from ischemic heart disease (IHD) were examined before and after coronary artery bypass grafting (CABG), there were 79 males and 46 females aged 45–74 years among them. Study blood samplings were performed a day before and then on the 1st, 3rd, 7th, and 12th day after the surgery. **Material and Methods:** Intra- and inter-group differences were estimated with Mann–Whitney U-test, Spearman's rank correlation and χ^2 test using application software SPSS v.16. Differences between parameters in case of deviation from null hypothesis and level of significance $P < 0.05$ were considered to be statistically significant. **Result and Discussion:** The levels of tumor necrosis factor-α (TNF-α) ($\chi^2 = 4.28$, $P < 0.05$, AUC = 0.91), interleukin (IL)-10 ($\chi^2 = 3.97$, $P < 0.05$, AUC = 0.829), and matrix metalloproteinases (MMP)-1 ($\chi^2 = 6.66$, $P < 0.01$, AUC = 0.963) were defined to be early and excessively increased before CABG and in early postsurgical period in patients with post-operative thromboembolic complications, suggesting the patients with IHD have a high risk of the complications mentioned above after CABG surgery. The association of TNF-α hyperproduction (above 30 pg/ml) on the 1st day after CABG and hemorrhagic complications development in patients after CABG was revealed ($\chi^2 = 4.0$, $P < 0.05$, AUC = 0.776). **Conclusion:** The maximum increasing of IL-6 level inpatients of all examined groups was present immediately after surgery, which was caused by surgical injury. The analysis of MMP-8 and MMP-9 did not reveal a correlation between their increased levels and the presence of complications in the patients after the surgery. The expression of the first tissue inhibitor of metalloproteinases was moderately increased in patients of all groups with no significant difference in its levels between the groups

Key words: Bypass surgery, cytokines, hemostasis, metalloproteinases, tissue inhibitor

INTRODUCTION

Coronary artery bypass grafting (CABG) is one of the most common heart surgery, which in fact decreases mortality in certain category of patients and improves quality of life in patients suffering from ischemic heart disease (IHD). However, post-operative morbidity is still essentially high, which is particularly related to multiple risk factors in patients.

In some authors' opinion, it is high levels of proinflammatory cytokines that are the important predictors of the development of the cardiovascular (CV) complications.[1,2] It was shown that high level of the

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tumor necrosis factor-α (TNF-α) after an extracorporeal circulation activates neutrophils and contributes to the activation of thrombotic status.[3] Relationship between risk of onset of myocardial infarction (MI), sudden cardiac arrest and myocardial ischemia after coronary artery bypass surgery and increased level of TNF was revealed.[4] At the same time, it was shown that in most of the patients with coronary atherosclerosis (60% vs. 40%) the serum level of TNF-α was not increased.[5] It was demonstrated that interleukin-6 (IL-6) induced releasing of Willebrand factor (WF),[6] which supports adhesion of leukocytes and platelets, and the higher levels of IL-6 led to higher releasing of WF[7] IL-6 supports activation of endothelium cells and monocytes and participates development of procoagulant reactions.

Prospective investigations revealed the high serum level of IL-6 was the significant predictor of IM development and the marker of lethal outcome in elderly persons.[8] One of the studies revealed the increasing of IL-10 level in patients with venous thrombosis in comparison with the control group.[9] In addition, Konenkov *et al*. (2016) and Shal'nev (2007) consider that IL-10 suppresses the tissue factor expression, therefore, inducing hypocoagulation and increasing plasminogen activator secretion.[10,11] According to other authors, decreasing of IL-10 serum level is associated with poor prognosis in patients with MI.[12]

The system of matrix metalloproteinases (MMP) and tissue inhibitors of metalloproteinases (TIMP), participating in regulation of the cardiac extracellular matrix condition, deserves attention among mechanisms of realization of impairing action of systemic inflammation factors. MMP-1 is one of the members of MMP family. It is released by few types of cells including endothelial cells of atheromatous plaque (AP) and can play a key role in vulnerable plaque rupture.[13] While it is the authors' opinion that MMP-8 is associated with AP growth progression with CV diseases [Figure 1] and

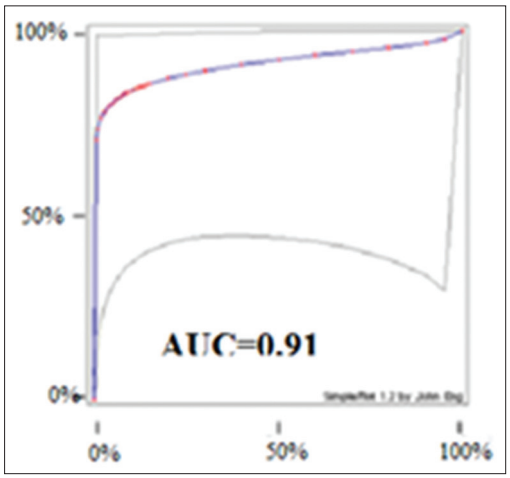

Figure 1: Receiver operating characteristic curve of estimation of tumor necrosis factor-α production in patients with thromboembolic complications after coronary artery bypass grafting in comparison with patients with ischemic heart disease with stable post-operative period

their complications, and is meant to be a potential marker for identifying the patients of high risk.[14] MMP-9 plays a crucial role in development and prognosis of MI.[15,16] The level of MMP-9 is increased in unstable plaques with synchronous decreasing of TIMP-1 activity.[17] Meanwhile, one of the investigations showed the plasma levels of MMP-9 to be significantly higher in coronary artery than in systemic blood flow in patients with acute MI.[18]

The data represented here suggest that the system of cytokines and metalloproteinases contributes to the regulation of the most of biochemical processes, which are essential for post-operative course in patients with IHD. However, despite a significant number of works available, authors' opinions are different and often controversial, while complex studies of cytokine profile and metalloproteinases system over time after CABG were not performed.

Objective of the study

The objective of the study was to define the amount and the role of changes in levels of TNF-α, IL-6, IL-10, MMP-1, MMP-8, MMP-9, and TIMP-1 in patients with IHD before and after CABG surgery and their contribution to genesis of complications in hemostasis system after myocardial revascularization.

MATERIALS AND METHODS

A total of 125 patients suffering from IHD were examined before and after myocardial revascularization by CABG surgery; there were 79 males and 46 females aged 45–74 years among them, mean age was 64 ± 0.9 years. All the patients were divided into four basic groups:

1. Patients with IHD and thromboembolic complications (TEC) after CABG surgery (acute MI, acute ischemic stroke, thromboembolism of intermediate and small pulmonary arteries) - 25 patients (Group I). TEC appeared on the 1st–2nd day after myocardial revascularization.
2. Patients with IHD and bleeding complications after CABG (passage of blood in drain tubes over 9 ml/kg in 12 h) - 26 patients (Group II).
3. Patients with IHD and laboratory abnormalities in hemostasis system (disturbances in vascular-platelet, coagulative, and fibrinolytic systems of hemostasis) after CABG surgery, but without clinically significant complications - 28 patients (Group III).
4. Patients with IHD and stable post-operative period - 46 patients (Group IV).

Control group included 30 healthy donors, comparable in age and sex.

Blood samplings were performed a day before surgery and then on the 1st, 3rd, 7th, and 12th day after CABG. The blood

serum was obtained by 10-min centrifugation at 1500 rpm, then the samples were tubed 1.0 ml each and stored at temperature-36°C. Assessment of the levels of TNF-α, IL-6, IL-10, MMP-1, 8, 9, and TIMP-1 was performed in blood serum by enzyme-linked immunosorbent assay using specific reagents ("R and D Diagnostics Inc.," USA). Results were stated in pg/ml and ng/ml. The data were present as a median and two quartiles (Me, Q_{25}, Q_{75}). For estimation of significance of changes in selected parameters and definition of optimal value for prognosis of complications development in patients with IHD after CABG, area enclosed by receiver operating characteristic (ROC)-curve and axis of false-positive classifications (AUC) was evaluated using software GraphPad Prism Software Inc., USA.

Study results

The changes of the levels of the investigated parameters in patients with IHD in comparison with a group of healthy volunteers are presented in Tables 1 and 2.

Statistically high levels of proinflammatory cytokines over the all study monitoring period in comparison with the control group were revealed [Table 1].

In Groups IV and III levels of TNF-α were 4–6 times higher at all monitoring points ($P < 0.05$–0.01) and were not different from the pre-operative levels on the 12th day. There was no statistically significant difference between the groups mentioned above [Table 1].

In Group II (with bleeding complications) the peak concentration of TNF-α (13 times increasing) was detected on the 1st day after the surgery and its serum level was statistically significant higher ($P < 0.001$) in comparison with the control group and other study groups (Groups I, III, and IV with $P < 0.05$). Its concentration was decreased later, coming up to 6–7 times higher in comparison with control group ($P < 0.01$) during the further monitoring. TNF-α level remained statistically higher ($P < 0.05$) in comparison with its pre-operative concentration on the 12th day too [Table 1]. To determine the existence of an association of TNF-α hyperproduction on the 1st day after the surgery with the development of bleeding complications on the 1st day χ^2 test was estimated. The level of significance was determined as 0.05 ($\chi^2 = 4.0$), thus the association between TNF-α hyper production on the 1st day (over 30 pg/ml) and development of bleeding in drain tubes at the same period was established. ROC-analysis confirmed [Figure 4] the aforesaid (AUC = 0.776).

In Group I (TE complications) the changes in TNF-α were the most undulated. Pre-operative level of TNF-α was 8 times higher in comparison with the reference range ($P < 0.01$) and significantly higher than in the other groups ($P < 0.05$). Further on the 1st day it showed relative reduction to 3-fold elevation ($P < 0.05$), then on the 3rd day its level increased again (10 times, $P < 0.01$), on the 7th day there was a certain decreasing of TNF-α level, and on the 12th day its concentration reached pre-operative values ($P < 0.01$) [Table 2]. To reveal a relationship or an independence between the provided parameters χ^2 test was estimated for TNF-αhyperproduction in the studied patients and the risk of TEC. The level of significance was determined as 0.05% ($\chi^2 = 4.28$, $P < 0.05$), thus the significant association between the TNF-αconcentration increasing above 24 pg/ml before CABG and development of TEC in the patients with IHD after CABG was revealed. ROC-analysis confirmed high diagnostic value of the THF-α increased level before CABG in terms of the risk of TEC development after CABG surgery (AUC = 0.91) [Figure 3].

Analysis of IL-6 level [Table 1] inpatients before and after CABG in Groups II and IV showed that its concentration was

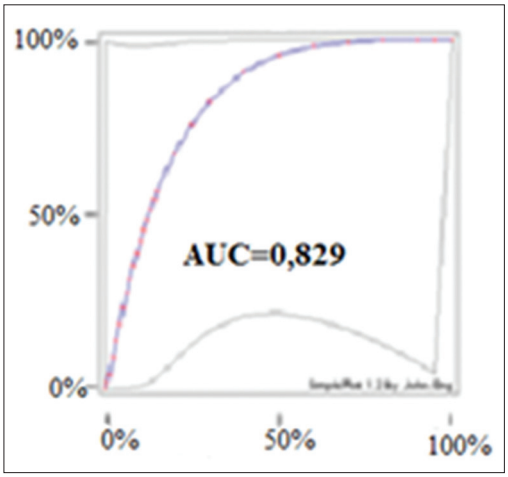

Figure 2: Receiver operating characteristic analysis of levels of expression of interleukin-10 of patients after myocardial revascularization in I and IV study groups

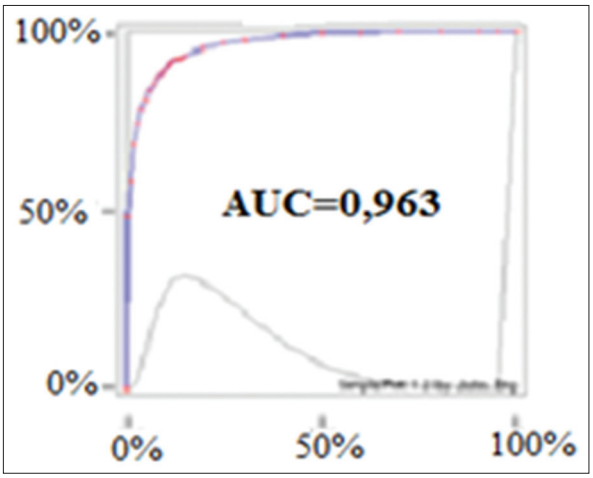

Figure 3: Receiver operating characteristic analysis of levels of matrix metalloproteinases-1 in blood sample of patients with ischemic heart disease and thromboembolic complications after myocardial revascularization with coronary artery bypass grafting surgery

Table 1: Levels of the proinflammatory or cytokines in blood serum of the studied patients with IHD before and after CABG and in the control group

Levels (Me; Q_{25}; Q_{75})	Patients with complications in hemostasis system (*n*=51)		Group III (*n*=28)	Group IV (*n*=46)	Control group (*n*=30)
	Group I (*n*=25)	Group II (*n*=26)			
TNF-α (pg/ml) before CABG	24.4**#×°↑ (22.4; 89.25) P1<0.05	9.5* (9.1; 32.13)	12.24* (2.7; 42.7)	9.46* (4.86;10.98)	2.8 (0.8; 10.9)
1st day after CABG	9.36*↓ (2.25; 20.7)	37.6***#"+(13.4; 92.8) P1,5,6<0.05	18.4** (8.9; 33.1)	10.8* (7.3; 24.5)	
3rd day after CABG	28.7** (17.5; 52.7) P5<0.05	17.85** (14.6; 35.1)	14.7* (5.2; 32.4)	17.4** (12.4; 53.6)	
7th day	11.7* (9.0; 46.8)	20.17** (15.4; 52.3) P3<0.05	13.7* (4.16; 35.7)	21.57** ↑ (11.1; 51.7) P3<0.05	
12th day	26.8** (21.6; 46.5) P7<0.05	23.0** (17.5; 38.5) P4<0.05	19.9** (16.5; 36.2)	16.02** (9.45; 29.7)	
IL-6 (ng/ml) before CABG	16.8* (13.6; 12.8)	13.2* (10.4; 53.4)	16.08* (14.5; 35.8)	15.75* ↑ (10.14;65.4)	2.32 (0.5; 9.4)
1st day after CABG	23.6***↑ (20.07; 34.07)	19.5** (13.46; 30.7)	38.78***↑ (25.6; 63.36) P1,5,6<0.0	22.54***↑ (19.9; 33.9)	
3rd day after CABG	37.5***↑ (31.6; 42.45) P2<0.05	21.86**↑(16.48; 38.3)	21.86**↑ (21.37; 39.63)	19.9** ↑ (17.16; 35.62)	
7th day	21.2** ×↑ (15.5; 29.2)	17.96** (15.97; 25.9)	9.28* (8.57; 10.8)	12.3* (9.75; 17.9)	
12th day	12.3* (10.12; 17.5)	13.6* (11.7; 28.5)	10.04* (7.8; 16.02)	9.28* (7.05; 50.05)	
IL-10 (pg/ml) before CABG	70.27*#×° (21.8; 274.38)	26.12(19.3; 115.3)	19.3 (16.6; 25.2)	21.5 (14.4; 32.1)	18.5 (16.7; 27.12)
1stday after CABG	322.79*×° (135.1; 654.6) P5,6,7<0.05	240.6*"+ (97.06;531.36) P1,5,6,7<0.05	32.9*↑ (27.3; 607.5)	64.79* (32.9; 328.49) P1,6,7<0.05	
3rd day after CABG	38.94* (23.23; 112.38)	48.97*" (26.26; 70.0)	19.6 (16.37;32.37)	44.16* (27.5; 68.65)	
7th day	22.69 (19.6; 38.99)	25.46 (23.5; 40.65)	17.3 (15.1; 29.6)	17.35 (17.12; 25.78)	
12th day	28.74 (21.96; 41.32)	19.3 (16.35; 138.2)	18.6 (17.02;25.34)	19.2 (8.6; 41.32)	

TNF-α: Tumor necrosis factor-α, CABG: Coronary artery bypass grafting, IHD: Ischemic heart disease

Table 2: Levels of the matrix metalloproteinases in blood serum of the studied patients with IHD before and after CABG and in the control group

Levels (Me; Q_{25}; Q_{75}) ng/ml	Patients with complications in hemostasis system (*n*=50)		Group III (*n*=30)	Group IV (*n*=50)	Control group (*n*=30)
	Group I (*n*=25)	Group II (*n*=25)			
MMP-1 before CABG	4.35**#x° (3.5; 7.5)	2.24* (1.5; 4.2)	2.22 (1.78; 3.18)	1.98 (1.34; 2.61)	1.1 (0.56; 3.3)
1st day after CABG	2.78* (2.3; 7.96)	2.06 (1.22; 4.75)	2.18 (1.84; 2.59)	2.07 (1.6; 2.31)	
3rd day after CABG	3.98#* (2.95; 9.5)	2.0 (1.25; 3.88)	2.12 (1.59; 2.72)	2.17 (1.74; 3.97)	
7th day	3.55**° (0.99; 6.45)	2.62 (1.68; 2.68)	3.19* (2.95; 3.47)	1.89 (1.59; 2.1)	
12th day	3.27** (3.14; 4.5)	3.98** (3.08; 7.07)	2.95** (2.75; 3.98)	2.1 (2.45; 4.46)	
MMP-8 before CABG	14.65*# (12.84; 27.53)	6.83* (6.29;17.65)	8.3** (6.62; 9.25)	9.34** (6.77; 13.09)	20.35 (20.08; 25.16)
1st day after CABG	16.59 (6.2; 45.48)	27.47 (15.46; 36.73) P1<0.05	28.85 (14.57; 36.3)	23.96 (16.22; 37.57)	
3rd day	36.17* (32.47; 51.23) P2<0.001	19.95 (18.57; 31.17) P2<0.05	27.01 (22.18; 43.0)	34.63 (23.75; 42.3)	
7th day	26.3 (18.6; 43.99)	26.6 (22.0; 32.51)	45.58** (30.4; 48.06)	26.6 (22.43; 26.65)	
12th day	32.39* (28.89; 41.7) P3<0.001	16.3 (12.49; 40.15) P3<0.05	10.96 (9.85; 14.72)	14.45 (11.67; 25.46)	
MMP-9 before CABG	144.7* (133.35; 374.42)	222.72 (136.73; 319.19)	215.32 (185.56; 279.1)	254.24 (191. 93; 301.42)	336.71 (229.69; 396.5)
1st day after CABG	284.04 (107.23; 476.89)	279.47 (227.13; 376.51)	280.25 (243. 36; 287.6)	240.25 (212.4; 306.05)	
3rd day	353.14 (190.2; 562.81)	377.93 (184.4; 468.7)	175.25 (140.18; 321.82)	340.01 (192.26; 401.5)	
7th day	301.6 (255.93; 320.11)	254.7 (205.7; 297.05)	254.7 (205.02; 297.05)	299.38 (269.73; 349.5)	
12th day	384.03 (295.89; 605.69)	348.8 (269.11; 467.55)	242.46 (213.56; 274.48)	319.03 (267.13; 355.0)	
TIMP-1 before CABG	247.2* (240.36; 346.5)	180.55 (165.92; 223.51)	278.79* (237.29; 329.38)	197.55 (142.57; 263.3)	169.12 (144.95; 191.1)
1st day after CABG	292.34** (277.68; 295.84)	273.82* (233.57; 320.37)	253.5* (235.43; 283.58)	235.4* (214.4; 258.86)	
3rd day	250.04* (210.87; 267.79)	242.31* (223.85; 267.78)	277.93* (231.16; 296.99)	268.79* (239.7; 278.13)	
7th day	215.69* (204.24; 232.77)	280.34** (244.57; 351.9)	310.2** (263.83; 321.99)	223.18 (201.78; 268.56)	
12th day	268.39* (210.38; 302.85)	275.78** (239.59; 326.55)	273.28* (236.19; 312.4)	212.73 (194.92; 247.15)	

Statistical confidence of difference of levels comparing with control group: *P<0.05, **P<0.01, ***P<0.001, statistical confidence of difference of levels between Groups I and II: #P<0.05, ##P<0.01, ###P<0.001, statistical confidence of difference of levels between Groups I and III: xP<0.05, xx$P$<0.01, xxx$P$<0.001, statistical confidence of difference of levels between Groups I and IV: °P<0.05, °°P<0.01, °°°P<0.001, - statistical confidence of difference of levels between Groups II and III: “P<0.05, “”P<0.01, “””P<0.001, statistical confidence of difference of levels between Groups II and IV: +P<0.05, ++P<0.01, +++P<0.001, statistical confidence of difference of levels between Groups III and IV: ▪P<0.05, ▪▪P<0.01, ▪▪▪P<0.001. Statistical confidence of difference of levels over the time: p1 (before CABG-1st day), p2 (before CABG-3rd day), p3 (before CABG-7th day), p4 (before CABG-12th day), p5 (1st–3rdday), p6 (1st–7th day), p7 (1st–12th day), p8 (3rd–7th day), p9 (3rd–12th day); p10 (7th–12th day). MMP: Matrix metalloproteinases, CABG: Coronary artery bypass grafting, IHD: Ischemic heart disease

8–9 times increased on the 1st and 3rd days after the surgery. Further its level decreased reaching the pre-operative values on the 12th day ($P < 0.05$). While in Groups I and III IL-6 concentration [Table 1] was 10–15 times increased on the 1st and 3rd days after the revascularization. Later its concentration decreased reaching the moderate elevated level on the 12th day, similar to the pre-operative value ($P < 0.05$).

In Group I IL-6 level was more increased on the 7th day after CABG ($P < 0.05$) as compared with its level in the patients of Group III [Table 1]. We did not reveal other statistically significant differences in IL-6 levels between the study groups.

During the characterization of IL-10 level in blood serum of patients in comparison with reference range, it was established, that in Group IV the level of IL-10 was moderately increased on the 1st and 3rd day after CABG ($P < 0.05$) with no further corresponding to that of the healthy people [Table 1]. In Group III level of IL-10 was insignificantly increased in comparison with reference range on the 1st day after the surgery only, its further concentration corresponded to the control one. In Group II level of IL-10 was also increased on the 1st and 3rd days after CABG, but its level on the 1st day was more than 6 times increased being higher than in Groups III and IV ($P < 0.05$), on the 3rd day its 2-fold increasing was detected with concentration significantly higher than in Group III ($P < 0.05$). Further, the level of IL-10 corresponded to the control one, reaching pre-operative value on the 12th day [Table 1]. In Group I (TE complications) the level of IL-10 before the revascularization was 3 times increased with the concentration being statistically higher than in Groups II, III, and IV ($P < 0.05$). On the 1st day after CABG the level of IL-10 was 7–8 times increased in comparison with the control group being higher than in Groups III and IV ($P < 0.05$), on the 3rd day concentration of IL-10, remained 2-fold increased, while on the 7th and 12th days it matched the reference range.

Estimation of χ^2 test confirmed the robust relationship between increasing of the IL-10 level above 65 pg/ml in pre-operative period and over 320 pg/ml on the 1st day after the surgery ($\chi^2 = 3.97$, $P < 0.05$) and the risk of TEC development in patients with IHD after myocardial revascularization by CABG surgery.

ROC-analysis of IL-10 level in the patients of Group I (TE complications) in comparison with its concentration in the patients of Groups IV (stable post-operative period), II, and III was performed. Estimated AUC was 0.829 (in comparison with Group IV, Figure 2), AUC = 0.663 (in comparison with Group II) and AUC = 0.932 (vs. Group III), be illustrative of the high level of IL-10, which we detected in the patients of Group I before surgery and in the early post-operative period in comparison with the other study groups, to be well specific and sensitive diagnostic value.

Analysis of the concentrations of matrix metalloproteinases and TIMP-1 [Table 2] revealed that in Group IV (stable post-operative period) MMP-1 level corresponded to that of control group during the all monitoring period, in Group III (laboratory abnormalities in hemostasis system without clinically significant complications in post-operative period) MMP-1 level before surgery, on the 1st and 3rd days did not differ from the control group values, while on the 7th and 12th days its 2.5–3-fold increasing was revealed ($P < 0.05$– 0.01). In Group II (bleeding complications in post-operative period) pre-operative level of MMP-1 was 2-fold increased ($P < 0.05$), further its level decreased to the control group values, and on the 12th day its 3,5-fold increasing in comparison with the healthy people group was detected again ($P < 0.01$).

In Group I (TE complications) MMP-1 concentration was 2,5–3,5-fold increase in comparison with control group during the all monitoring period ($P < 0.05$–0.01) with its level before CABG being higher ($P < 0.05$) than in the other study Groups II, III, and IV. On the 3rd and 7th days its level was higher ($P < 0.05$) in comparison with its concentration in Groups II and IV correspondingly [Table 2]. Revealed increasing of the MMP-1 level in blood serum of the patients with detected post-operative TE complications forced estimation of this marker as a predictor of the development of complications mentioned above. Significant relationship between increased concentration of MMP-1 before and after CABG and development of TEC was detected. ROC-analysis confirmed the foregoing (AUC = 0.963).

Levels of MMP-8 in Groups IV and III did not differ from the control group level during the all monitoring period [Table 2]. In Group II its value was detected to be statistically low (3 times) before surgery ($P < 0.05$), while in the post-operative period its concentration reached the control group level during the all monitoring period.

In Group I MMP-8 level before CABG was, on the one hand, 1.4-fold decreased in comparison with the healthy

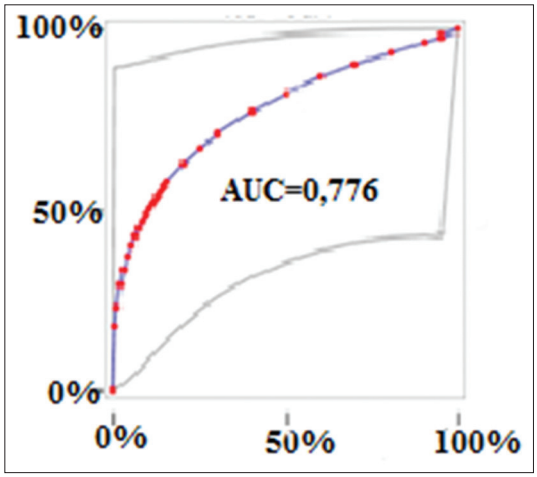

Figure 4: Receiver operating characteristic analysis of levels of tumor necrosis factor-α in blood sample of patients after coronary artery bypass grafting with bleeding complications in comparison with stable post-operative period

people ($P < 0.05$), but on the other hand it was 2 times higher in comparison with its pre-operative level in patients of Group II ($P < 0.05$). This category of patients showed undulated profile of MMP-8 concentration in post-operative period [Table 2]: On the 1st and 7th days its value corresponded to the control group, but on the 3rd and 12th days it was increased by 1,5 times ($P < 0.05$). The analysis of relationship between increased level of MMP-8 and development of TE complications in patients with IHD after CABG did not confirm such correlation ($\chi^2 = 0.53$; $P > 0.05 < 0.25$).

The concentration of MMP-9 in Groups IV, III, and II did not differ from the level of the healthy volunteers during the all monitoring period, while in Group I low level of MMP-9 was detected before CABG ($p<0.05$), further its concentration was similar to the reference range.

Level of TIMP-1 in Groups I and III with complications was increased ($P < 0.05–0.01$) during the all monitoring period, in Group II its value was statistically increased in comparison with the reference range during the post-operative period, while in Group IV (with stable post-operative period) its moderate increasing ($P < 0.05$) was shown on the 1st and 3rd days after CABG only.

DISCUSSION

We confirmed the data, according to which the high level of proinflammatory cytokines (TNF-α) is a predictor of CV complications development, which we detected in patients of Group I with TEC after CABG. Unfortunately, we did not find the data in literature concerning changes of TNF-α in the patient after CABG in case of bleeding complications development in the post-operative period, but we revealed significant association of its hyperproduction and development of bleeding in drain tubes (pleural and pericardial) over 9 ml/kg in the immediate 12 h of post-operative period. Hyperproduction of TNF-α in early post-operative period in patients with bleeding complications is primary by nature being a reaction to surgical injury, hypoxia, and extracorporeal circulation (not physiological), which is associated with such complications in hemostasis system ($\chi^2 = 4.0$; $P < 0.05$, AUC = 0.776, Figure 4).

It was reported that the level of IL-6 was increased after protamine injection and reached maximum level in 3 h after CABG. IL-6 concentration remains higher than pre-operative one in 24 h after CABG.[19,20] Thus, we confirmed the results of the study according to which IL-6 increases during and just after the EC, which is caused by surgical injury, and decreases on the 3rd–5th days after the surgery but further remaining of its increased values is the evidence of significance of systemic inflammatory reaction[21] and can be used for prognosis of course of inpatient period.

Authors consider at the high level of MMP-1 in the patients with coronary atherosclerosis is a risk factor of the onset and development of acute coronary syndrome, because MMP-1 contributes to injury to APs, where later clotting occurs.[22,23] Our study show edits statistically significant increasing during the all monitoring period - before and after the surgery in the group of patients with TEC after CABG, which confirms the authors' opinions.

MMP-8, known as collagenase-2 or neutrophil collagenase, is associated with inflammatory conditions. It is released by neutrophils, endothelial and smooth muscle cells and macrophages. In authors' opinion, the low level of MMP-8 correlates with the degree of activity of atherosclerotic injury, accompanied with the decrease of macrophages and increase of collagen level in atherosclerotic lesions.[24] The decreased level of MMP-8 was detected (1,5-fold, $P < 0.05$) before CABG surgery in comparison with healthy people both in groups with clinical complications in post-operative period, with laboratory abnormalities in hemostasis system, and in group with a stable post-operative period. Revealed trends are possibly caused by taking medications from statin group (simvastatin and atorvastatin) in therapeutic dose be patients of all the four groups.

We did not confirm the data of authors according to which MMP-9 was a marker of CVD[25] and its increased value is associated with high risk of CV events.[26,27]

The study showed the changes of the elements of the system of MMP and TIMP-1 in the patients with IHD to be oppositely directed. TIMP strongly combine with MMP and irreversibly inactivate them. Expression of the TIMP is enhanced in the focuses of inflammation,[28] which we detected in groups with complications in the post-operative period and also in group with a stable post-operative period in the early post-operative period.

CONCLUSION

1. Revealing of early and excessive increasing of TNF-α over 24 pg/ml in pre-operative period, IL-10 over 65 pg/ ml before surgery and above 320 pg/ml on the 1st day after the surgery, and concentration of MMP-1 more than 3, 3 ng/ml before and after CABG indicates a high risk of TE complications in patients with IHD after CABG surgery.
2. Association between hyperproduction of TNF-α (over 30 pg/ml) on the 1st day after CABG and development of bleeding in drain tubes on the same post-operative day ($\chi^2 = 4.0$ when $P < 0.05$) is revealed. ROC-analysis confirmed this association (AUC = 0.776).
3. Assessment of IL-6 concentration in patients with IHD before and after CABG confirmed the authors' data, according to which its level increased during and just after EC, caused by surgical injury, and decreased on the 3rd–5th day after the surgery, while further remaining of its increased level was the evidence of significance

of systemic inflammatory reaction in patients with complications in post-operative period.

4. Taking into consideration the biologic role of MMP and TIMP-1, we may conclude that disbalance in this system leads to structural damage of myocardial extracellular matrix, contributing to cardiac remodeling, and myocardial fibrosis.

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