

YENİ BİOMARKERLAR

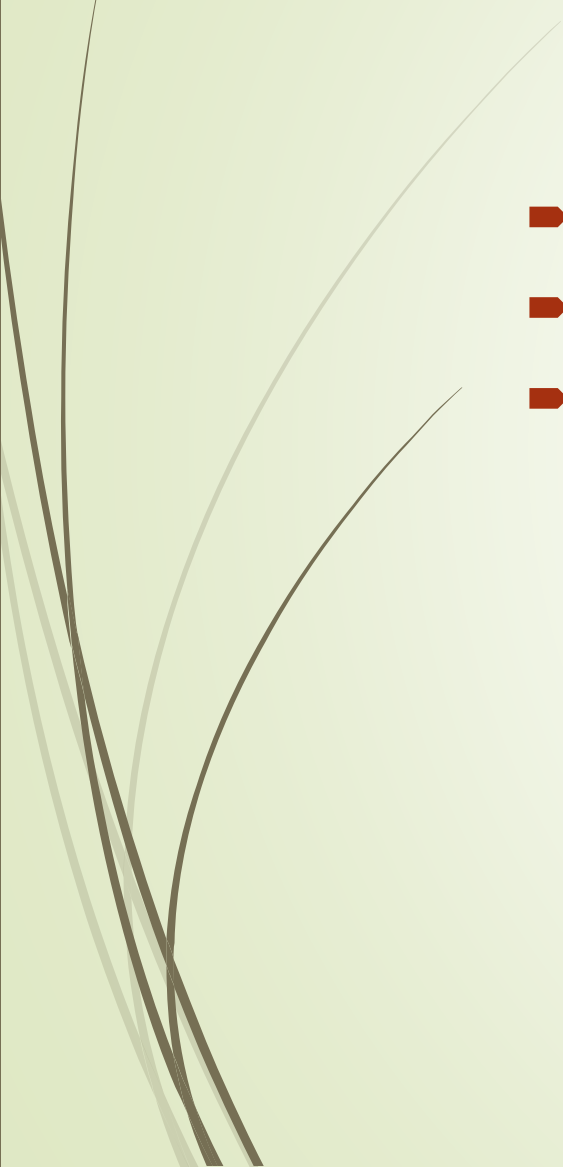
22. ACİL TIP BAHAR SEMPOZYUMU

Uz. Dr. Serhat Ör n

Bandırma Devlet Hastanesi



Sunum Planı

- İdeal biyomarker özellikleri
 - En sık araştırılan konular 2017
 - Öne çıkan biyomarkerlar
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İdeal Biyomarkerın Özellikleri

- Ait olduğu sistemin dışındaki bozukluklardan etkilenmemeli
- Analizi pahalı donanımlar gerektirmemeli
- Biyomarkerın sonuçları kolaylıkla yorumlanabilmeli
- Genel popülasyonda miktarı yaygın bir varyasyon göstermemeli
- Hastalığın durumu için kesin, hassas ve spesifik olmalı
- Ölçümü pratik ve kolay, düzeyleri hastalığın evreleri ile uyumlu olmalı
- Vücut doku ve sıvılarından uygun, güvenilir miktarda temin edilmeli

İdeal Biyomarker; FDA

- Spesifik

- Yüksek doku / serum oranı

- Doku dışında olmayan, hatta patolojik olarak mevcut değildir

- Sensitif

- Sıfır taban çizgisi

- Prediktif

- Kanda uzun yarılanma ömrü

- Tersinirlik göstergesi verir

- Yaralanma derecesine orantılı salınım

- Gücü

- Hızlı, basit, doğru ve ucuz tespit

- İnvaziv olmayan / erişilebilir

Sıkça Araştırılan Konular

- Sepsis
- Akut koroner sendromlar
- SVH ve Kafa travmaları
- Kanseri tanı ve tedavi araştırmaları

Öne Çıkan Biyomarkerlar

- Presepsin
- Neopterin
- Copeptin
- C-MyC
- GPBB
- IL-10
- NRGN, NSE ve MT3 paneli



Presepsin

- CD14 çözünür hali (sCD14)
- Monosit ve makrofaj yüzeyinden salınır
- Glikoprotein yapıda
- LPS-LBP kompleksinin reseptörüdür
- Bakteriyel enfeksiyona ait endotoksin sinyalini
TLR-4 vasıtasıyla transdüksiyona sokmak

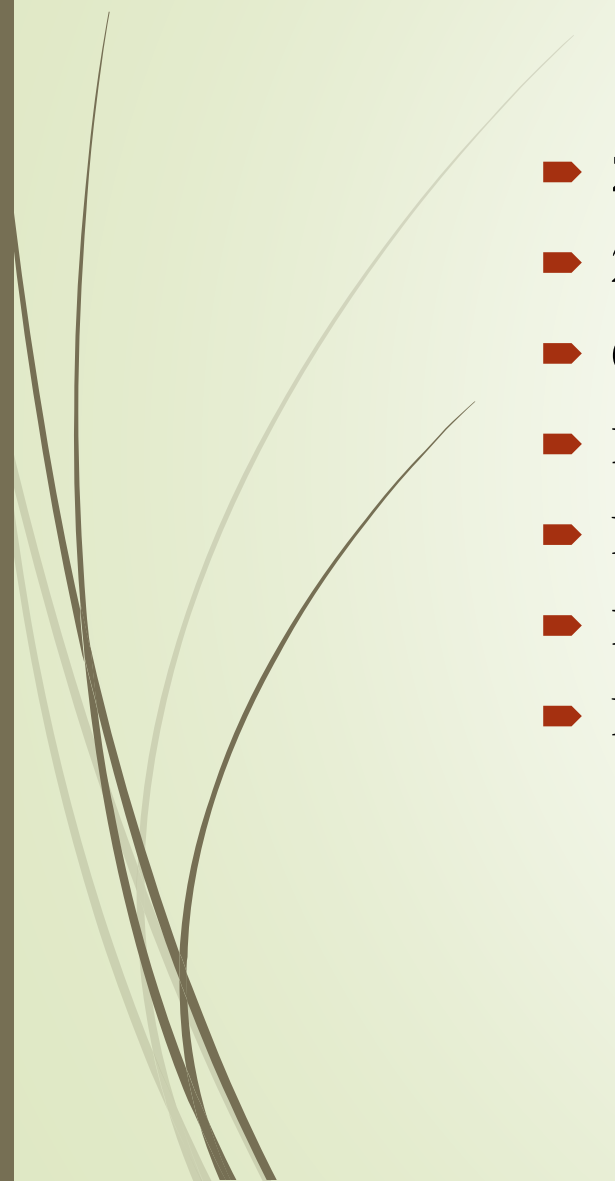
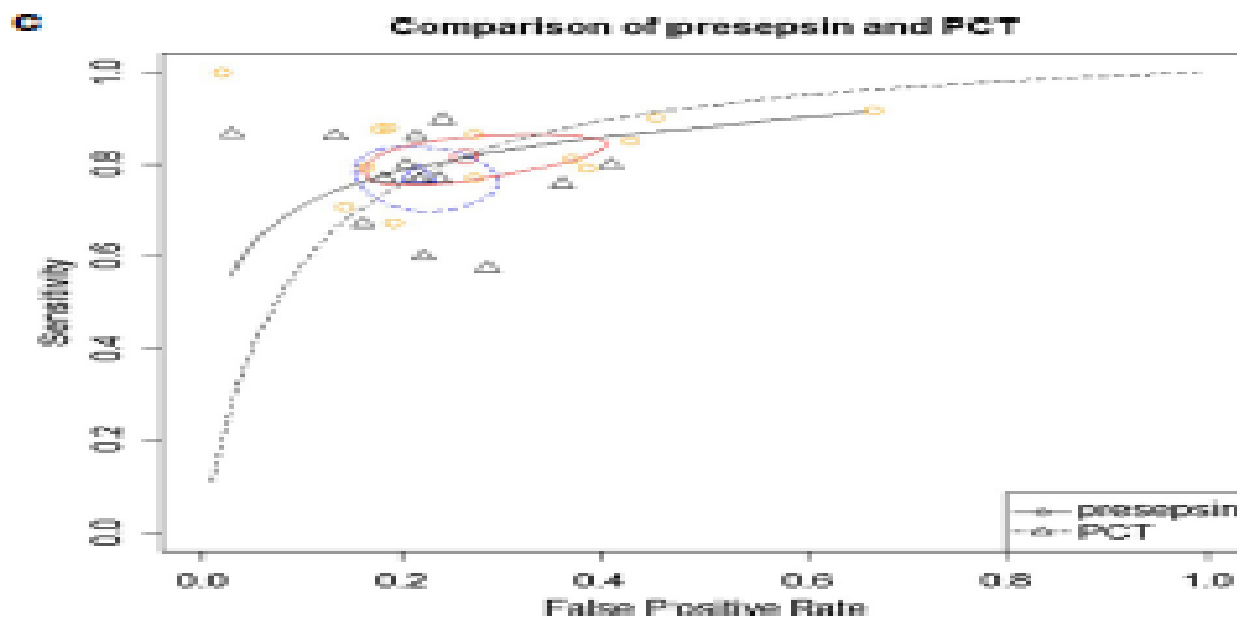
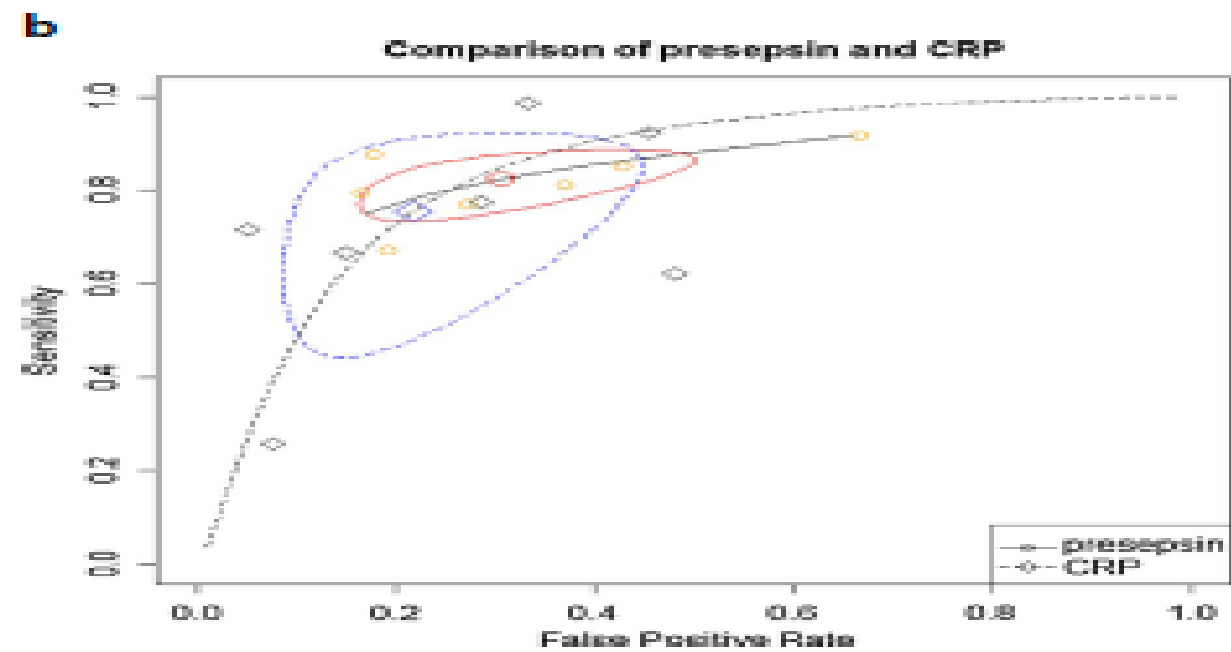
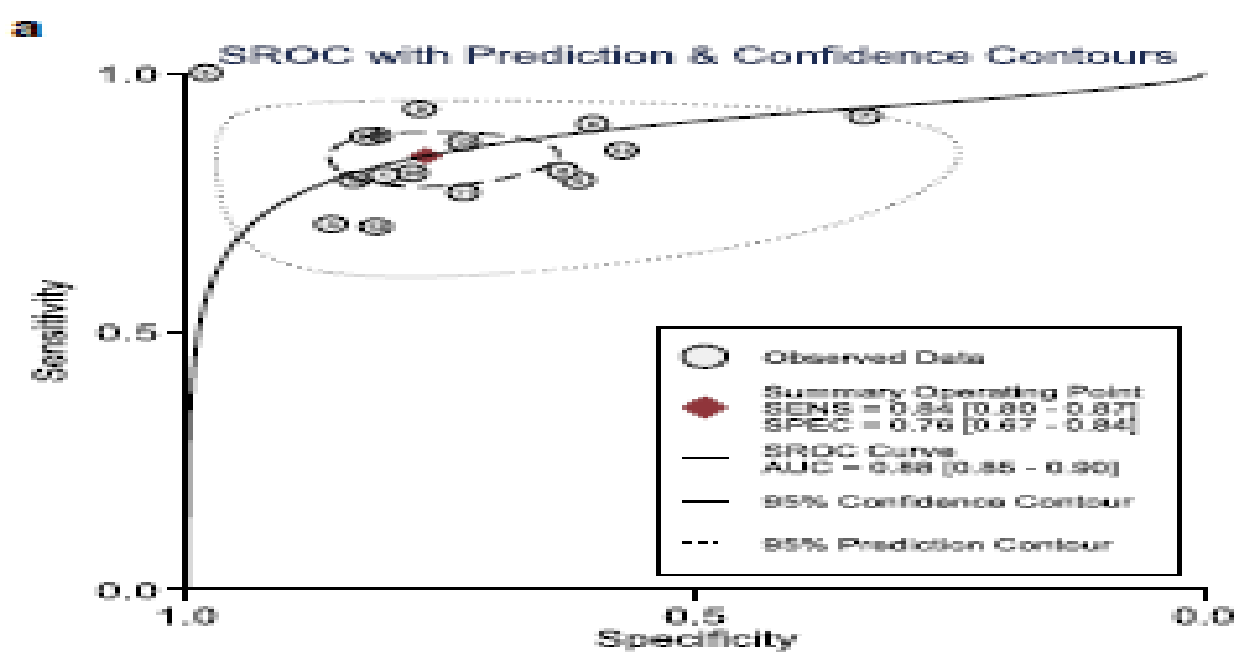
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- 2002'de ilk olarak Japonya'da keşfedildi
 - 2015 yılında, ilk meta-analiz
 - Cut off 600 – 650 pg/ml
 - PCT gibi sepsis tanısı için umut verici
 - kombinasyon halinde daha yararlı olabilir
 - Prognoz ve mortalite tahmininde yardımcı
 - kardiyak cerrahi, hemofagositik sendrom veya böbrek yetmezliği

Table 6 Summary diagnostic accuracy of the included studies for biomarkers, presepsin, procalcitonin, and C-reactive protein

References	Sepsis/control (n)	Presepsin			Procalcitonin			C-reactive protein		
		Sensitivity	Specificity	AUC	Sensitivity	Specificity	AUC	Sensitivity	Specificity	AUC
Shozushima et al. [17]	101/41	0.80	0.81	0.88	–	–	0.65	–	–	0.82
Endo et al. [29]	115/70	0.88	0.81	0.91	0.86	0.79	0.91	–	–	–
Liu et al. [33]	680/279	0.71	0.86	0.82	0.60	0.78	0.72	–	–	–
Ulla et al. [38]	106/83	0.79	0.67	0.70	0.89	0.76	0.88	–	–	–
Vodnik et al. [39]	30/100	1	0.98	0.99	0.87	0.97	0.96	–	–	0.96
Behnes et al. [25]	81/15	0.90	0.60	0.84	–	–	0.86	–	–	–
Brenner et al. [26]	60/60	0.91	0.67	0.83	0.77	0.78	0.84	0.67	0.85	0.79
Romualdo et al. [35]	37/189	0.81	0.63	0.75	0.76	0.64	0.79	0.62	0.52	0.60
Ishikura et al. [31]	43/39	0.93	0.76	0.89	–	–	–	–	–	–
Kweon et al. [32]	73/45	0.88	0.82	0.94	0.86	0.87	0.92	0.99	0.67	0.85
Cakir Madenci et al. [27]	26/11	0.77	0.76	0.83	0.76	0.79	0.85	0.92	0.58	0.82
Nakamura et al. [34]	37/75	0.70	0.81	0.78	–	–	–	–	–	–
Sargentini et al. [36]	60/44	0.86	0.72	0.89	0.80	0.80	0.91	–	–	–
Godnic et al. [30]	40/7	0.85	0.63	0.71	0.58	0.67	0.63	0.77	0.75	0.73
Takahashi et al. [37]	359/97	0.80	0.82	0.89	0.77	0.76	0.85	0.72	0.95	0.82
Carpio et al. [28]	114/9	0.81	0.75	0.83	–	–	–	–	–	–
Kada Klouche et al. [41]	100/44	0.90	0.55	0.75	0.80	0.59	0.80	–	–	–
Romualdo et al. [40]	70/130	0.67	0.81	0.78	0.67	0.84	0.82	0.26	0.92	0.59

AUC, area under the receiver operating characteristic curve; –, not report



Note: The red circle represents the summary estimate for presepsin, the blue triangle represents the summary estimate for PCT, and the blue diamond represents the summary estimate for CRP. The ellipse represents the confidence region for each summary estimate.

Fig. 5 **a** Hierarchical summary receiver operating characteristic plot of presepsin across all included studies. **b** Comparisons of presepsin and C-reactive protein with summary receiver operating characteristic curves. **c** Comparisons of presepsin and procalcitonin with summary receiver operating characteristic curves. Note the red circle represents the summary estimate for presepsin, the blue triangle represents the summary estimate for procalcitonin, and the blue diamond represents the summary estimate for C-reactive protein. The ellipse represents the confidence region for each summary estimate

İlk 30 günlük mortalite

Table 2. Prediction of mortality according to the first sampling (≤ 24 hours) of presepsin.

Study	Mortality (%)	AUC (95% CI)	Cutoff, ng/L	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Liu 2013 [13]	28 d (34)	0.658 (0.614–0.703)	556	62.2	66.8	48.3	78.0
Behnes 2014 [14]	30 d (50)	0.64 (0.54–0.75)					
Masson 2014 [15]	ICU (57)	0.72 (0.61–0.82)	1631	70.2	67.4	74.1	63.0
Carpio 2015 [17]	30 d (19)	0.743	825	86	65	37.3	95.0
Ali 2016 [18]	28 d (58)	0.891 (0.765–1.000)	957.5	94.7	85.7	90.0	92.3
El-Shafie 2017 [20]	IH (36)	0.755 (0.938–0.571)					
Kim 2017 [21]	30 d (19)	0.684 (0.605–0.756)	2455	76.5	53.7	31.3	89.2

Abbreviations: d, days; ICU, intensive care unit; IH, in-hospital; CI, confidence interval; PPV positive predictive value; NPV, negative predictive value.

<https://doi.org/10.1371/journal.pone.0191486.t002>



Neopterin

- IFN gama uyarısıyla monosit / makrofajlar
- IL-4, IL-10 ve IL-12 salınımını inhibe eder
- Hücresel yanıt erken ve duyarlı
- Özgüllüğü düşük
- Cut off 16,4 nmol/L
- Lokalize enfeksiyonlardan etkilenmez
- Kalıcı inflamasyon ve sistemik enfeksiyon

- Yükselmesi klinik görünümünden önce
- Hücre tepkisinin kritik olduğu klinik vakalar
- Sepsis tanısında ve prognozda umut verici
- KOAH'da akut alevlenme/ topl. KP ayrımı
- Bakteriyel ve viral orijin arasında ayırım

Sensitivity

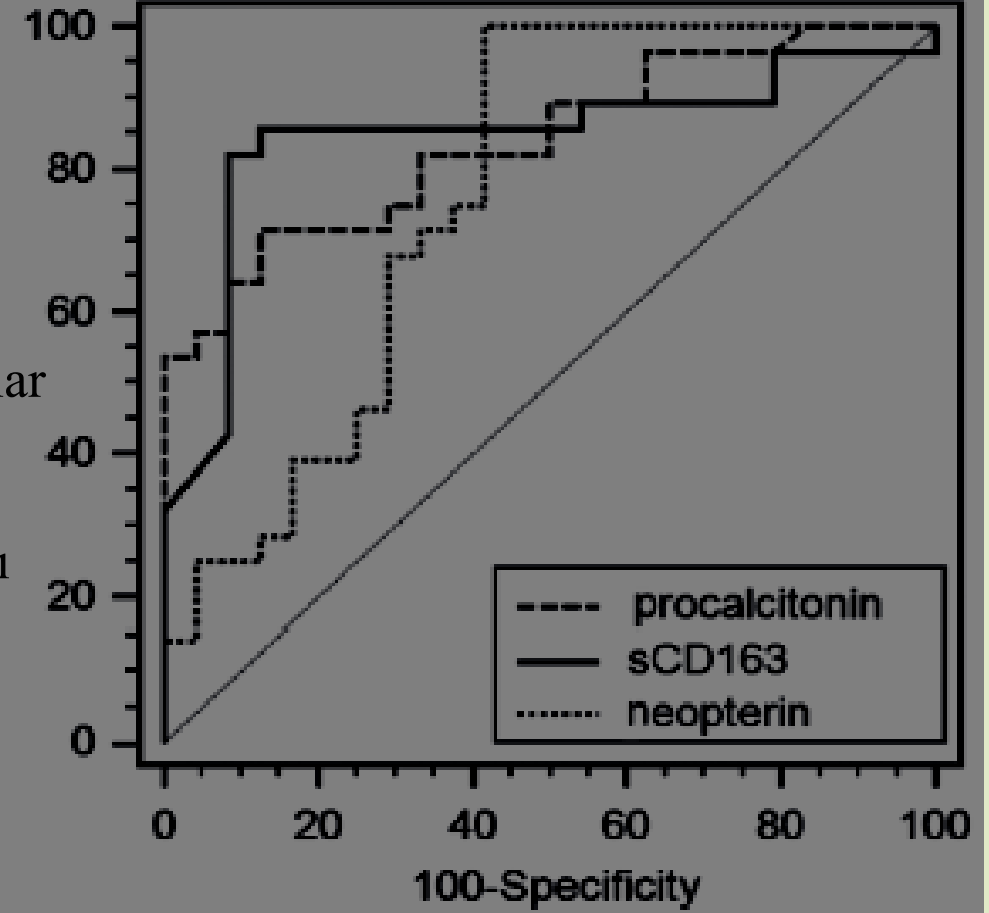


Fig. 4. PCT, sCD163 and NPT ROC curves

Table 3. ROC curve data for PCT, sCD163 and NPT

Marker	AUC	Sensitivity (%)	Specificity (%)	Standard error	95% CI	Cut-off value
PCT	0.840	71.4	87.5	0.0542	0.712–0.927	4.58 ng/mL
sCD163	0.847	82.1	91.7	0.0599	0.720–0.932	1.146 mg/L
NPT	0.763	100.0	58.3	0.0708	0.625–0.870	16.4 nmol/L

Table 4. Comparison of ROC curves

	sCD163 vs. NPT	sCD163 vs. PCT	PCT vs. NPT
Difference between areas	0.0833	0.00670	0.0766
Standard error	0.0802	0.0796	0.0704
95% confidence interval	–0.0739 to 0.241	–0.149 to 0.163	–0.0613 to 0.215
z statistic	1.039	0.0842	1.089
Significance level	p = 0.2990	p = 0.9329	p = 0.2761

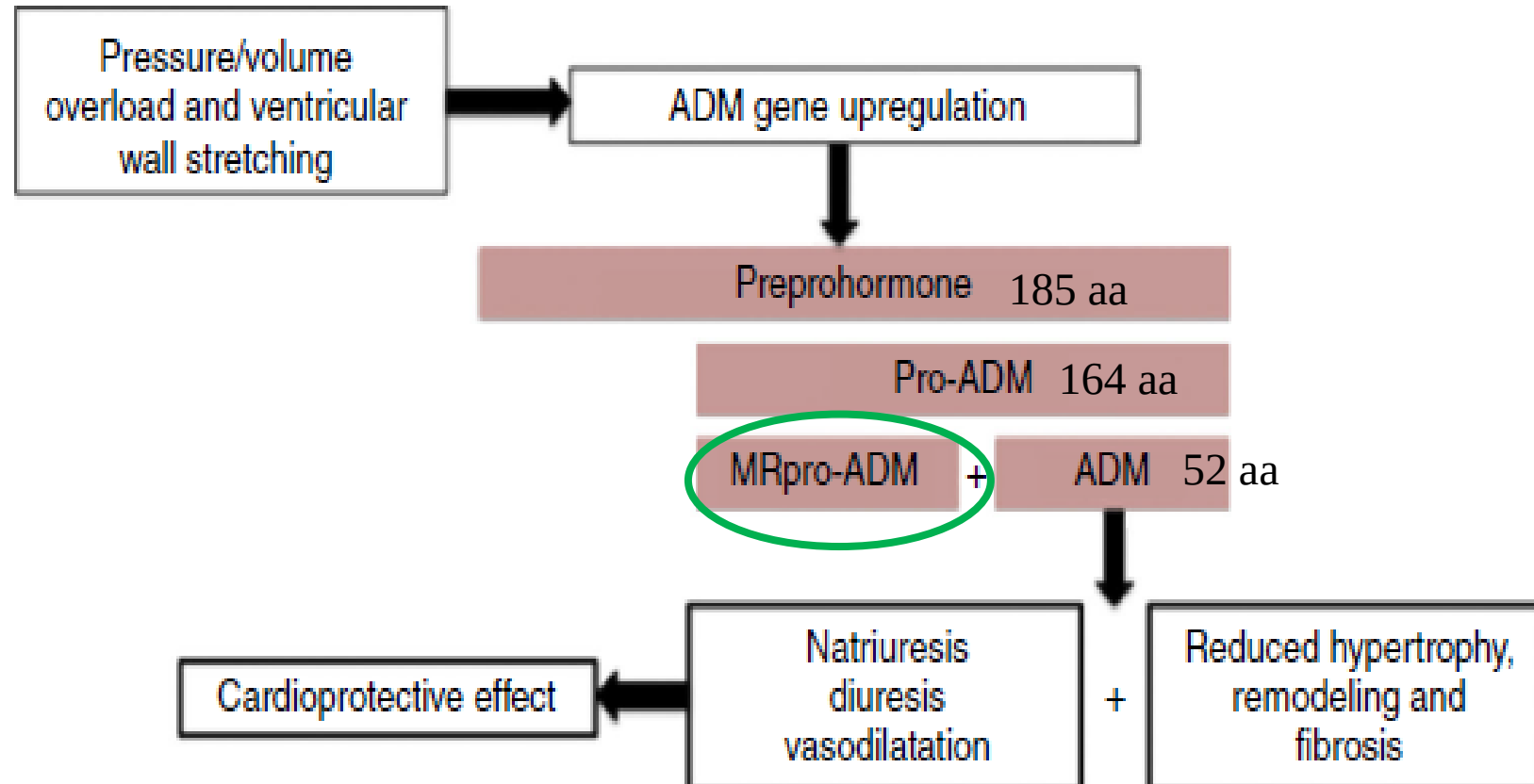
Table 4 Number of isolates and levels of PCT, CRP, and neopterin according to the microorganism isolated

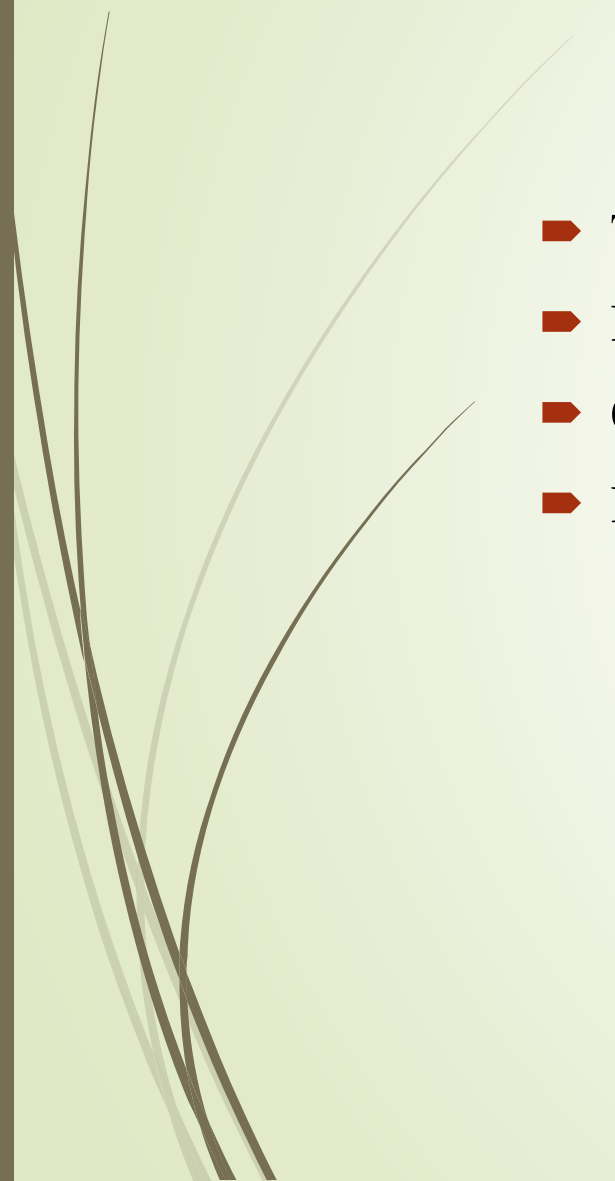
Microorganism isolated	Number isolates (%)	PCT (ng/mL) median (IQR)	CRP (µg/mL) median (IQR)	Neopterin (ng/mL) median (IQR)
<i>Haemophilus influenzae</i>	27 (35.6)	0.09 (0.08–0.14)	69.8 (23.89–160.9)	15.7 (8.34–23.19)
<i>Pseudomonas aeruginosa</i>	14 (18.4)	0.11 (0.05–0.23)	78.75 (19.42–181.5)	15.02 (11.39–17.89)
<i>Moraxella catarrhalis</i>	9 (11.8)	0.07 (0.04–0.09)	77.63 (46.8–157.9)	9.87 (6.32–15.64)
Enterobacteria	6 (7.9)	0.20 (0.07–0.44)	101.6 (27.83–364.92)	18.02 (12.89–30.17)
<i>Streptococcus pneumoniae</i>	15 (19.8)	0.14 (0.07–0.42)	133.4 (74.77–285.97)	12.42 (6.8–20)
<i>Staphylococcus aureus</i>	2 (2.6)	0.44	307.95	10.83
<i>Aspergillus fumigatus</i>	2 (2.6)	0.15	172.73	16.81
Co-infection <i>S. pneumoniae</i> and <i>H. influenzae</i>	1 (1.3)	0.34	310.7	21.07

Abbreviations: CRP, C-reactive protein; IQR, interquartile range; PCT, procalcitonin.

MR Pro ADM

- ADM kalsitonin geniyle ilgili 52 amino asitlik bir peptittir.
- Çok çeşitli dokularda sentezlenmekte
- Vazodilatasyona neden olur
- Diürezis ve natriürez uyarır kb düşürür
- Normal plazma düzeyi 1-10 ng/ml
- 1.6 nmol / L mortalite ve NIMV'yi tahmin
- 2.5 nmol / L YBÜ'e kabulünü tahmin



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- Toplum kökenli pnömonide; PSI ve CURB-65 ile
 - Prognoz ve Mortalite tahmininde
 - CURB-65 ile kombinasyon
 - PCT ile kombinasyonu sepsis tanısında yardımcı

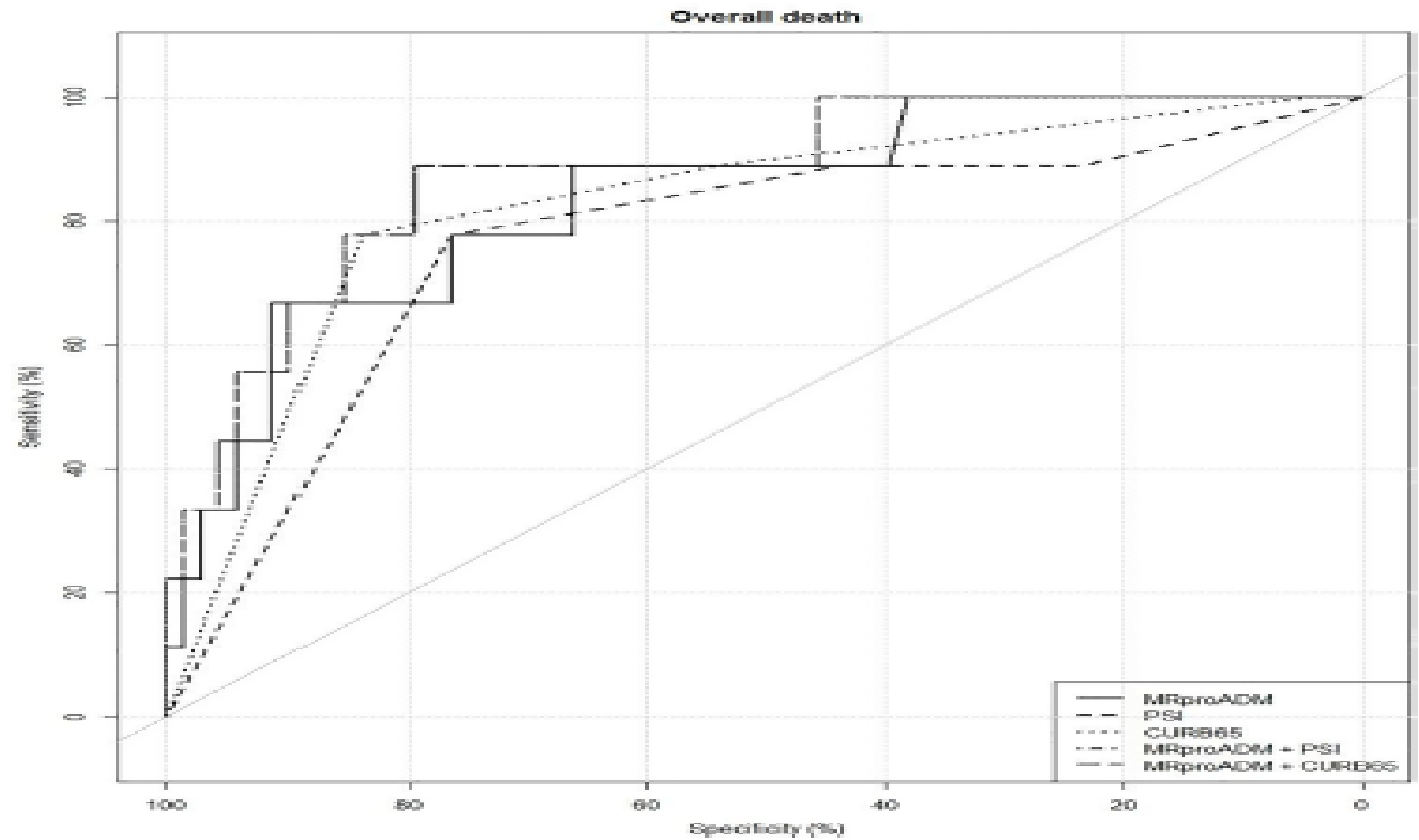


Fig 3. Predictive performance of MRproADM in combination with PSI or CURB65 for overall death.

<https://doi.org/10.1371/journal.pone.0157002.g003>

Table 3 Occurrence of the primary and secondary outcomes according to the clinical risk score and MR-proADM

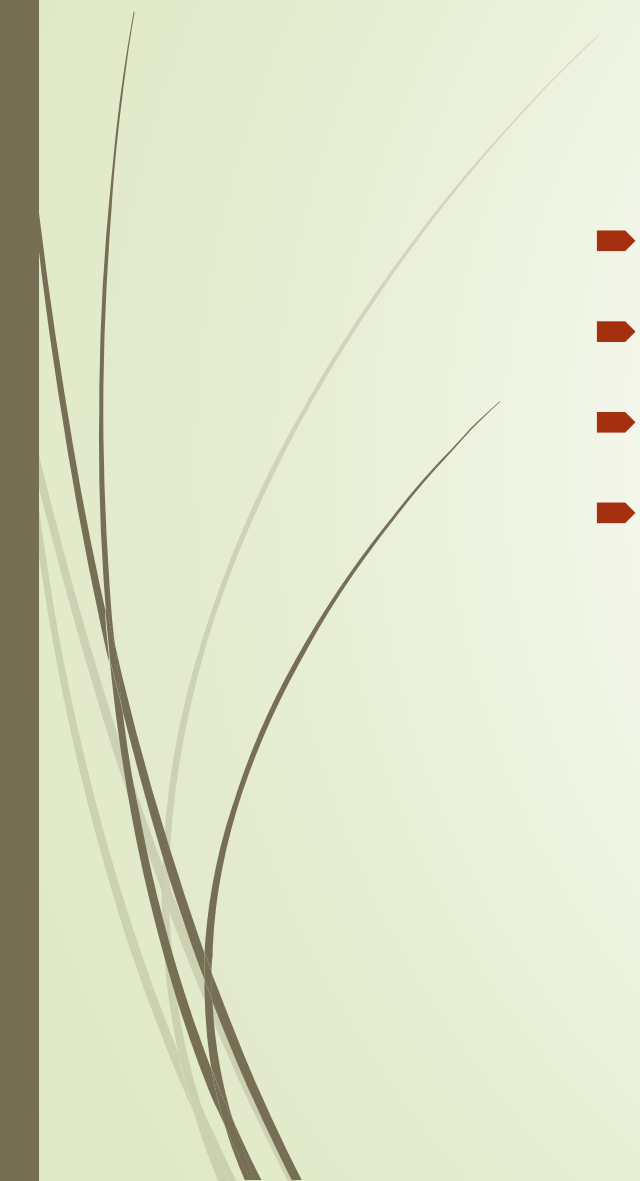
Biomarkers and outcomes	Clinical risk score			P-value	MR-proADM		P-value
	Low risk (n=44)	Intermediate risk (n=113)	High risk (n=120)		<1.13 nmol/L* (n=203)	≥1.13 nmol/L (n=74)	
MR-proADM, nmol/L	0.74 (0.57–0.89)	0.83 (0.62–1.12)	0.95 (0.75–1.29)	<0.0001	0.75 (0.58–0.90)	1.49 (1.26–1.99)	–
Copeptin, pmol/L	9.66 (3.53–27.16)	12.43 (6.35–33.62)	17.66 (6.38–33.62)	0.013	–	–	–
At day 30							
Death, n (%)	2 (4.5)	3 (2.7)	9 (7.5)	0.28	8 (3.9)	6 (8.1)	0.013
ICU transfer, n (%)	2 (4.7)	9 (8.0)	14 (11.9)	0.37	11 (5.5)	14 (19.2)	0.001
New ECOPD, n (%)	4 (9.3)	14 (12.5)	17 (5.8)	0.62	22 (11.1)	13 (18.6)	0.17
Primary end point, n (%)	7 (15.9)	24 (21.2)	35 (29.2)	0.15	36 (17.7)	30 (40.5)	0.0002
At day 7							
Death, n (%)	0 (–)	0 (–)	6 (5.0)	0.028	2 (1.0)	4 (5.4)	0.046
ICU transfer, n (%)	1 (2.3)	8 (7.1)	12 (10.0)	0.27	9 (4.5)	12 (16.2)	0.002
New ECOPD, n (%)	1 (2.3)	6 (5.3)	3 (2.5)	0.56	6 (3.0)	4 (5.4)	0.47
Secondary end point, n (%)	2 (4.7)	13 (11.5)	19 (15.8)	0.15	15 (7.4)	19 (25.7)	0.0001

Note: *The cutoff of 1.13 nmol/L was the threshold of MR-proADM providing the best combination of sensitivity and specificity for the occurrence of the primary end point.

Abbreviations: ECOPD, exacerbation of COPD; ICU, intensive care unit; MR-proADM, mid-regional pro-adrenomedullin.

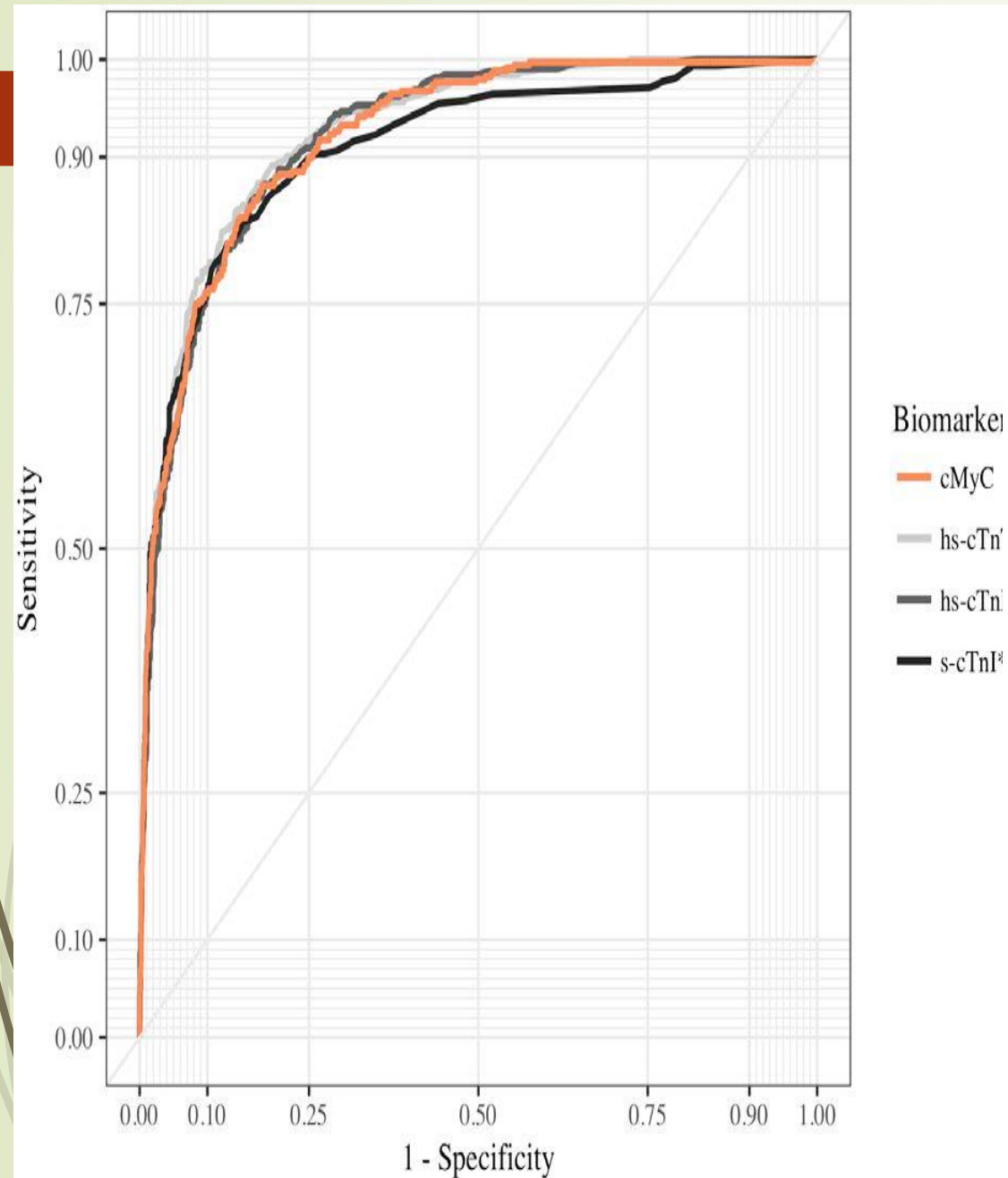
Copeptin

- Arjinin vasopressin (AVP) prekürsörü
- C-terminal fragmanı stabil ve kolay ölçülen bir peptit
- AMI hızla yükselir, 2-5 gün içerisinde geriler
- Cut off 14 pmol / L
- N-STEMI HscTnT ve copeptin kombinasyonu
- % 97.7 duyarlılık, % 99.03 npv, % 55.9 diagnostik özgüllükle dışladı

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- Aks'de kombine edilmesi stratejisi,
 - Acil serviste% 40 uzun süreli kalmayı önleyebilir
 - KOAH; akut atak ve prognoz değerlendirilmesinde
 - Diyabetin prognoz değerlendirmesinde

MBP-C

- Offer ve ark. tarafından 1973'te keşfedildi
- Yavaş iskelet, hızlı iskelet ve kalp kasına özgü 3 izoformdan oluşur
- Serum konsantrasyonu hızlı yükselir ve troponin T ve I'dan daha hızlı düşer
- ≤ 10 ng / L rule-out, $120 \leq$ ng / L rule-in eşiği
- Hs-cTnT'ye göre daha yüksek duyarlılık, hs-cTnI için benzer duyarlılık
- Göğüs ağrısı 3 saatin altında olan (erken sunum yapan) hastalar için daha efektif



Initial model	New model - MyC (10/120) - chest pain for <3hrs					
hs-cTnT	No AMI (n=382)			AMI (n=78)		
	Rule-out	Observe	Rule-in	Rule-out	Observe	Rule-in
	99	28	0	0	1	0
	83	161	6	0	38	10
	0	0	5	0	1	28
NRI	0.128 (95% CI, 0.055-0.181)			0.128 (95% CI, 0.044-0.213)		
NRI (dimensionless)	0.256 (95% CI, 0.157-0.356); p value <0.001			IDI	0.086 (95% CI, 0.052-0.119)	
Thresholds	Sensitivity (95% CI)		NPV (95% CI)	Specificity (95% CI)		PPV (95% CI)
hs-cTnT 5 ng/L	98.8% (95.8-100%)		99.2% (97.5-100%)	33.3% (28.6-38.1%)		23.3% (19-27.9%)
hs-cTnT 52 ng/L	37.2% (25.9-48.2%)		88.5% (85.3-91.4%)	98.7% (97.5-99.7%)		86.1% (73.3-96.9%)
cMyC 10 ng/L	100% (100-100%)		100% (100-100%)	46.4% (41.5-51.6%)		27.5% (22.3-32.5%)
cMyC 120 ng/L	49% (36.8-60%)		90.4% (87.4-93.2%)	97.2% (95.3-98.7%)		77.8% (65.2-89.7%)

Initial model	New model - MyC (10/120) - chest pain for <3hrs					
hs-cTnI	No AMI (n=381)			AMI (n=79)		
	Rule-out	Observe	Rule-in	Rule-out	Observe	Rule-in
	76	11	1	0	0	0
	109	169	4	0	39	8
	0	5	6	0	4	28
NRI	0.257 (95% CI, 0.185-0.310)			0.051 (95% CI, -0.032-0.133)		
NRI (dimensionless)	0.308 (95% CI, 0.210-0.406); p value <0.001			IDI	0.101 (95% CI, 0.067-0.135)	
Thresholds	Sensitivity (95% CI)		NPV (95% CI)	Specificity (95% CI)		PPV (95% CI)
hs-cTnI 2 ng/L	100% (100-100%)		100% (100-100%)	23.2% (19-27.1%)		21.3% (16.8-25.7%)
hs-cTnI 52 ng/L	40.3% (29.5-51.2%)		88.7% (85.5-91.7%)	97.2% (95.5-98.7%)		74.8% (60.7-87.5%)
cTnI 10 ng/L	100% (100-100%)		100% (100-100%)	47.1% (42.4-52.2%)		28.2% (22.9-33.3%)
cMyC 120 ng/L	45.6% (34.7-57.3%)		89.6% (86.7-92.6%)	97.1% (95.3-98.7%)		76.6% (64.1-87.8%)

Legend: NRI = Net Reclassification Improvement; IDI = Integrated Discrimination Improvement; CI = Confidence Interval; NPV = Negative Predictive Value; PPV = Positive Predictive Value; AMI = Acute Myocardial Infarction, based on the adjudicated gold-standard diagnosis

Table 3. Net Reclassification Improvement: hs-cTnT (Validation Cohort)

Initial Model	New Model—cMyC (10/120)—Validation Cohort					
hs-cTnT	No AMI (n=1089)			AMI (n=219)		
	Rule-Out	Observe	Rule-In	Rule-Out	Observe	Rule-In
Rule-out	249	77	0	0	1	0
Observe	190	509	32	1	66	24
Rule-in	0	7	25	0	9	118
NRI	0.081 (95% CI, 0.029–0.113)			0.068 (95% CI, 0.016–0.121)		
NRI (dimensionless)	0.149 (95% CI, 0.089–0.210); <i>P</i> value <0.001			IDI		0.050 (95% CI, 0.029–0.070)
Thresholds						
hs-cTnT 5 ng/L	Sensitivity (95% CI): 99.6% (98.5–100)		NPV (95% CI): 99.7% (99–100)	Specificity (95% CI): 29.9% (27.3–32.5)		PPV (95% CI): 22.2% (19.6–24.8)
hs-cTnT 52 ng/L	Sensitivity (95% CI): 58.1% (51.6–64)		NPV (95% CI): 92% (90.5–93.5%)	Specificity (95% CI): 97.1% (96.1–98)		PPV (95% CI): 80.1% (73.2–86.2)
cMyC 10 ng/L	Sensitivity (95% CI): 99.5% (98.6–100)		NPV (95% CI): 99.8% (99.3–100)	Specificity (95% CI): 38.8% (35.8–41.7)		PPV (95% CI): 24.6% (21.8–27.4)
cMyC 120 ng/L	Sensitivity (95% CI): 64.9% (58.5–71.2)		NPV (95% CI): 93.1% (91.4–94.5)	Specificity (95% CI): 94.8% (93.5–96)		PPV (95% CI): 71.5% (64.7–78)

AMI indicates acute myocardial infarction, based on the adjudicated gold-standard diagnosis; CI, confidence interval; IDI, integrated discrimination improvement; NPV, negative predictive value; NRI, net reclassification improvement; and PPV, positive predictive value.

Table 4. Net Reclassification Improvement: hs-cTnI (Validation Cohort)

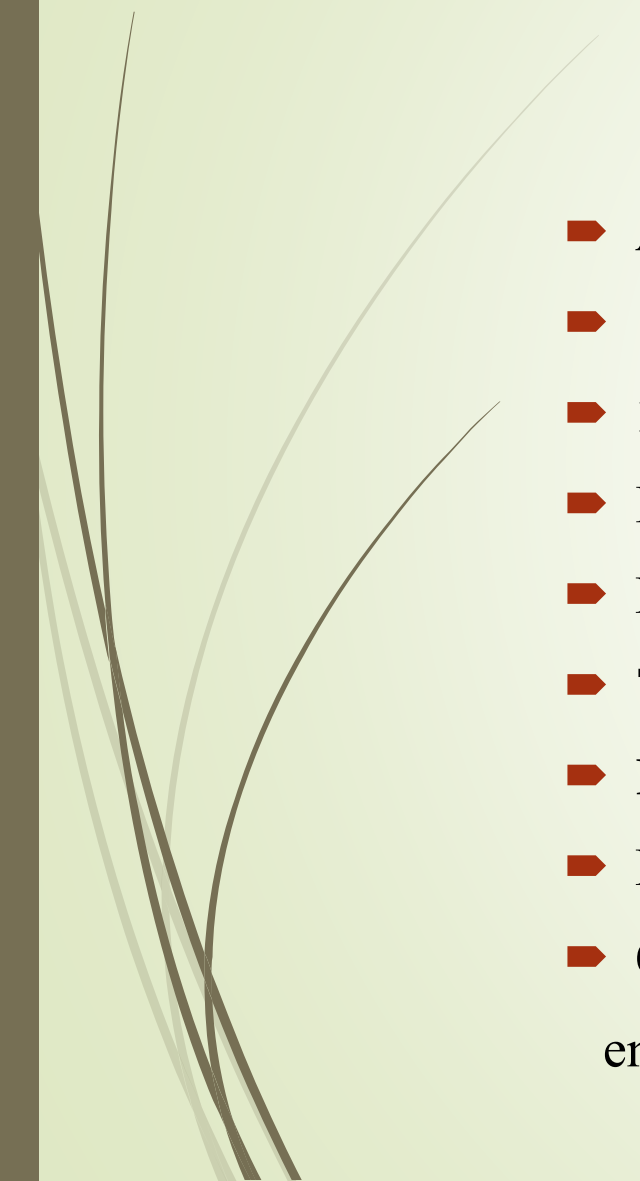
Initial model	New model—cMyC (10/120)—Validation cohort					
hs-cTnI	No AMI (n=1080)			AMI (n=224)		
	Rule-out	Observe	Rule-in	Rule-out	Observe	Rule-in
Rule-out	167	32	0	0	0	0
Observe	273	526	22	1	63	19
Rule-in	0	25	35	0	16	125
NRI	0.226 (95% CI, 0.174–0.258)			0.009 (95% CI, –0.044–0.062)		
NRI (dimensionless)	0.235 (95% CI, 0.174–0.296); <i>P</i> value <0.001			IDI		0.078 (95% CI, 0.057–0.098)
Thresholds						
hs-cTnI 2 ng/L	Sensitivity (95% CI): 100% (100–100)		NPV (95% CI): 100% (100–100)	Specificity (95% CI): 18.4% (16–20.8)		PPV (95% CI): 20.3% (18–22.7)
hs-cTnI 52 ng/L	Sensitivity (95% CI): 62.9% (56.4–68.9)		NPV (95% CI): 92.5% (90.9–93.9)	Specificity (95% CI): 94.5% (93–95.8)		PPV (95% CI): 70.4% (63.6–76.5)
cMyC 10 ng/L	Sensitivity (95% CI): 99.6% (98.6–100)		NPV (95% CI): 99.8% (99.3–100)	Specificity (95% CI): 39.4% (36.3–42.4)		PPV (95% CI): 25.5% (22.9–28.5)
cMyC 120 ng/L	Sensitivity (95% CI): 64.3% (58.1–70.7)		NPV (95% CI): 92.8% (91.2–94.3)	Specificity (95% CI): 94.7% (93.2–96)		PPV (95% CI): 71.8% (65.3–77.9)

AMI indicates acute myocardial infarction, based on the adjudicated gold-standard diagnosis; CI, confidence interval; IDI, integrated discrimination improvement; NPV, negative predictive value; NRI, net reclassification improvement; and PPV, positive predictive value.



GPBB

- Glikojenolizin anahtar enzimidir
- GP'nin üç ana izoenzimi var: beyin (BB) kas (MM) karaciğerde (LL)
- GPBB glikojen ve sarkoplazmik retikulum ile ilişkilidir
- İskemi esnasında parçalanır sarkoplazma salınır
- Glikojenoliz ve plazma membran bütünlüğünde (geçici) değişikliklerle sonuçlanır

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- Akut SVH ve TİA
 - 172 hastada plazma GPBB düzeyleri incelenmiş
 - 12 saat içinde ve 48 ± 24 saatte ölçüm
 - İlki 46.3 ± 38.6 ng / ml ve ikinci ölçümde 38.6 ± 36.5 ng / ml
 - Her ikisi için $p < 0.01$
 - 7.0 ng / mL
 - ROC eğrisi altındaki alan 0.96 (% 95 GA 0.93-0.98)
 - Duyarlılık ve özgüllük % 93
 - GPBB konsantrasyonu ile klinik sonuç ya da enfarktüs hacmi arasında korelasyon yok

IL-10

- Anti-inflamatuar sitokin
- aktive edilmiş makrofajlar ve Th2 hücreleri tarafından üretilir.
- kafa travmasında belirteç
- S100B ile kıyaslama
- 233 pg/mL
- <6 saat hem de <24 saatte yüksek tanısal etkinlik

Table 4. IL-10 and S100B capacity to differentiate CT scan results in patients younger and older than 65.

Age	Protein	Cut-off	n CT -	n CT +	p-value	% SE (95% CI)	% SP (95% CI)
≥ 65	IL-10	0.210	22	14	0.004	100 (100–100)	31.8 (13.6–50.0)
	S100B	0.091	22	14	0.013	100 (100–100)	36.4 (18.2–59.1)
< 65	IL-10	0.1606	89	8	0.144	100 (100–100)	28.1 (19.1–37.08)
	S100B	0.071	89	8	0.052	100 (100–100)	19.1 (11.2–28.1)

<https://doi.org/10.1371/journal.pone.0193278.t004>

NRGN, NSE ve MT3 paneli

- Panel kullanımına örnek
- Etkinlik ve maliyet?
- NRGN, NSE ve MT3 cut off 0.041, 0.033, 0.018 ng/ml
- mTBI'yi makul (% 72-100) doğrulukla tanımlamaktadır
- hasar şiddetinin bir göstergesi olarak geliştirilebilir

TABLE 3 | ROC curve analysis for performance of top panels in discriminating mild TBI from controls, listed by statistical method and features included.

Method	Features included	AUC	Sensitivity	Specificity	PPV	NPV
Random forest (RF)	Neurogranin (NRGN), neuron-specific enolase (NSE), metallothionein 3 (MT3), age, sex	0.91	0.98	0.72	0.84	0.96
RF	NRGN, NSE, MT3	0.91	0.98	0.71	0.83	0.96
Logistic regression (LR)	NRGN, NSE, MT3, age, sex	0.87	0.97	0.53	0.75	0.93
LR	NRGN, NSE, MT3	0.88	0.97	0.53	0.75	0.93

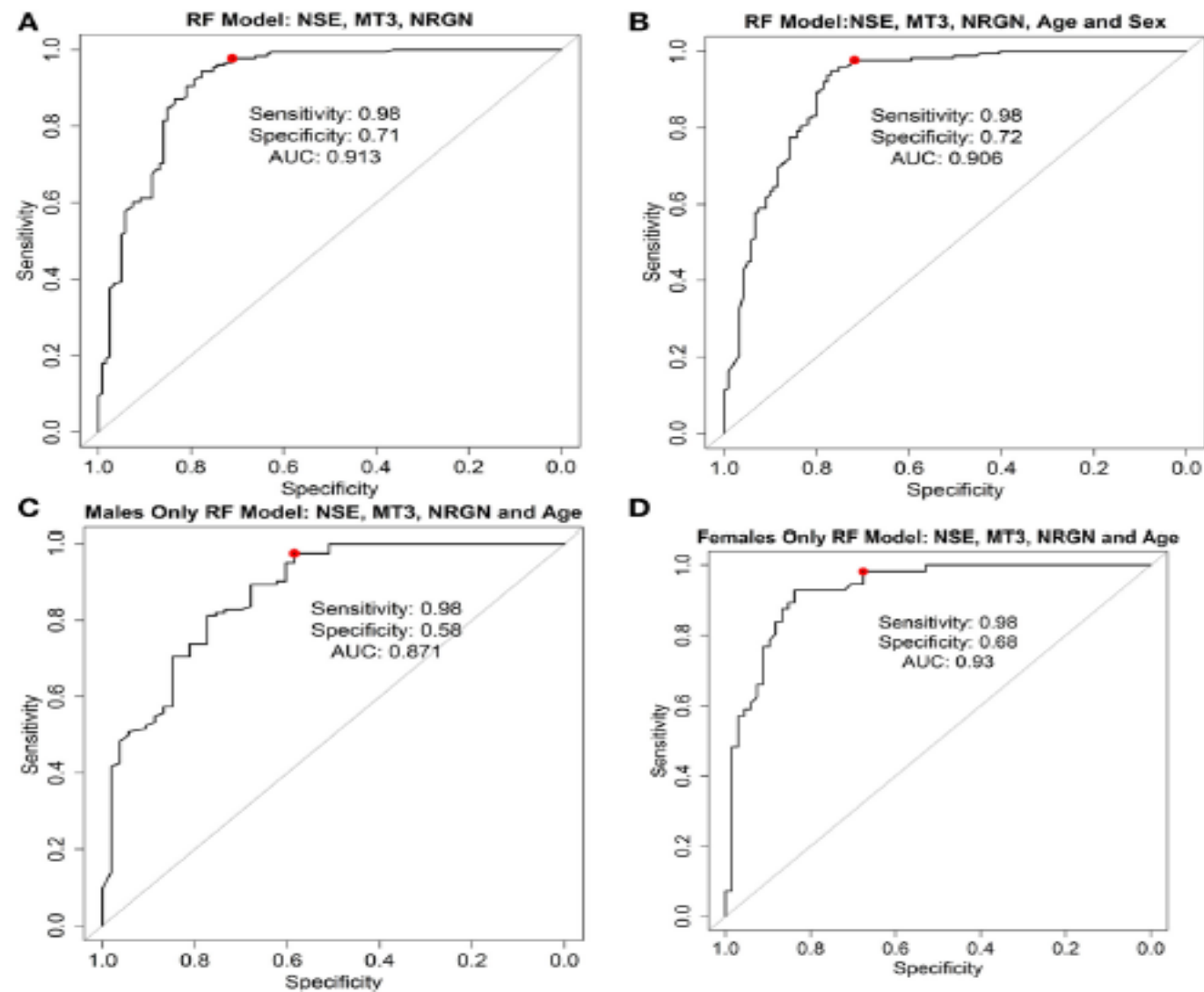
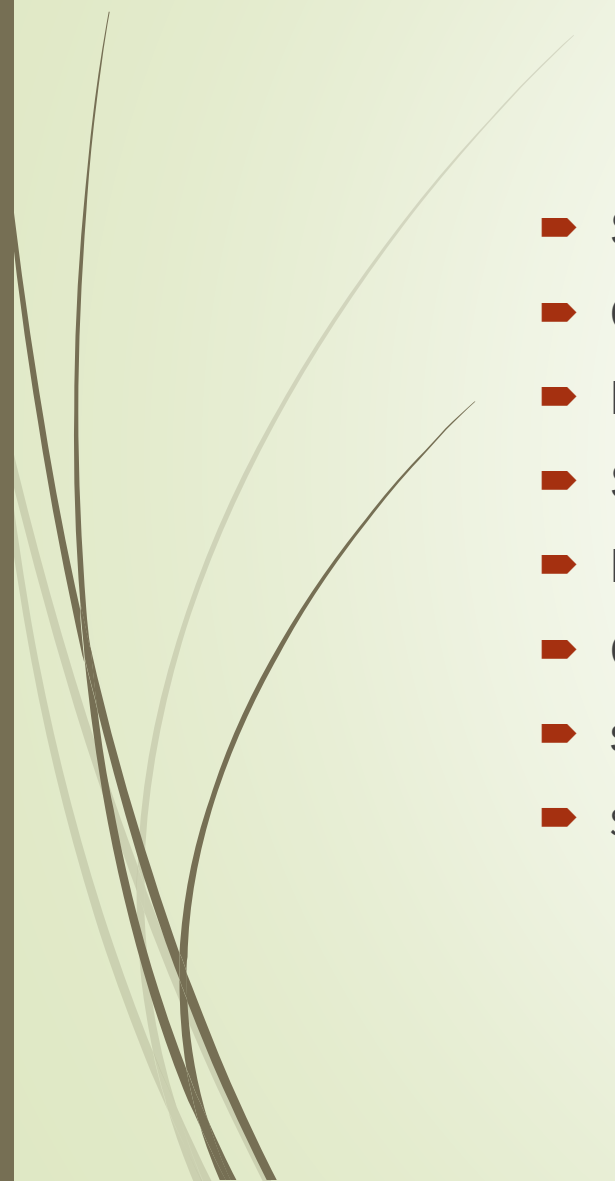
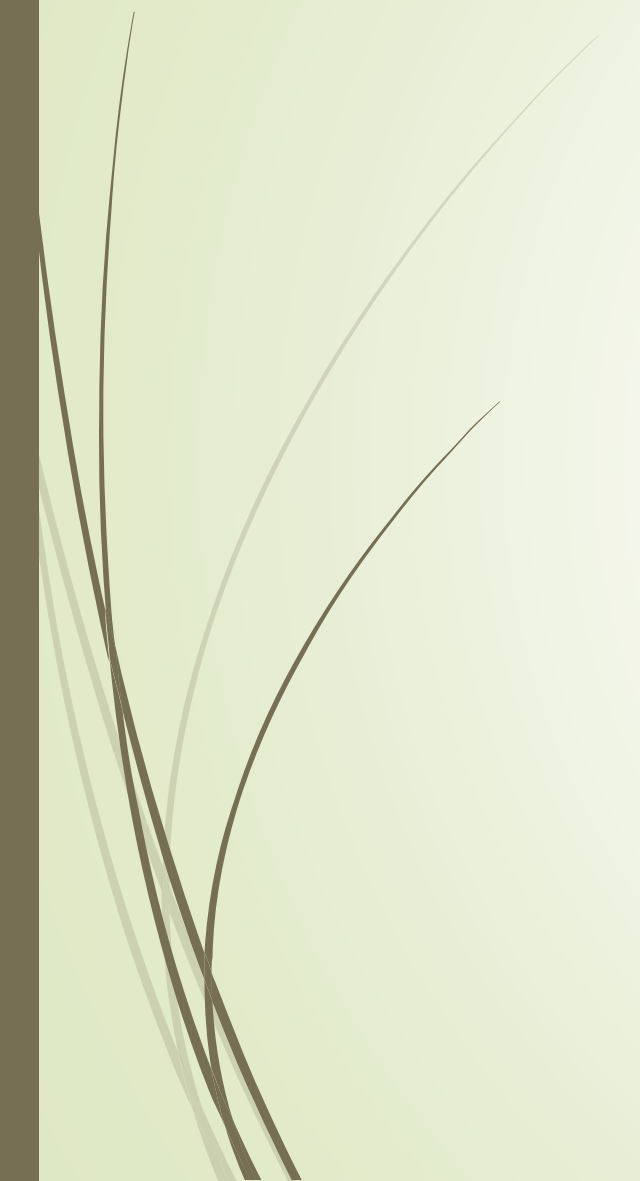


FIGURE 5 | Receiver operator characteristic curves for random forest (RF) models. ROC curve analysis showing plotted models built using three biomarkers neurogranin (NRGN), metallothionein 3 (MT3), and neuron-specific enolase (NSE) only **(A)**, three biomarkers with age and sex as covariates in the model **(B)**, biomarkers and age in the male patients only **(C)**, and biomarkers and age in female patients only **(D)**. The red dot indicates the threshold point for the reported optimal sensitivity (0.98) and the corresponding specificity for classifying mild TBI versus healthy controls. Area under the curve (AUC = C-statistic; CI, confidence intervals for each AUC estimate) is indicated for each panel.

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- SIRT2
 - CXCL10
 - MIP-1alpha
 - SLAMF1
 - MCP-1
 - CCL4
 - sCD163
 - sST2



➡ **Teşekkürler..**