BUKTI KORESPONDENSI

ARTIKEL JURNAL INTERNASIONAL BEREPUTASI Q3

Judul	Correlation Beetwen Blood Serum PSA Level and MMP-2 in Prostate Adenocarcinoma
Nama Penulis	**Anny Setijo Rahaju (Sebagai Penulis Utama dan corresponding author),** Aniek Meidi, Gondo Mastutik, Sjahjenny Mustokowati, Arifa Mustika
Nama Jurnal	Indonesian Journal of Urology Vol. 23 No. 02, July 2016
Penerbit	Ikatan Ahli Urologi Indonesia (IAUI)
26 Januari 2023	Submit Artikel melalui web JURI : https://juri.urologi.or.id/juri
Indeks	Accredited No. 158//E/KPT/2021 (Sinta 2) https://sinta.kemdikbud.go.id/journals/profile/884
ISSN	0853-442X & E-ISSN 2355-1402
Link artikel	https://juri.urologi.or.id/juri/article/view/220
Submitted	25 Oktober 2015
Artikel diterbitkan	20 April 2016
Judul Desertasi dan tahun lulus	MEKANISME ANTI KANKER METFORMIN TERHADAP VIABILITAS SEL KARSINOMA UROTHELIAL KANDUNG KEMIH (CELL LINE 5637) MELALUI miRNA-4257 DAN AMPK 23 November 2021 (tahun lulus)
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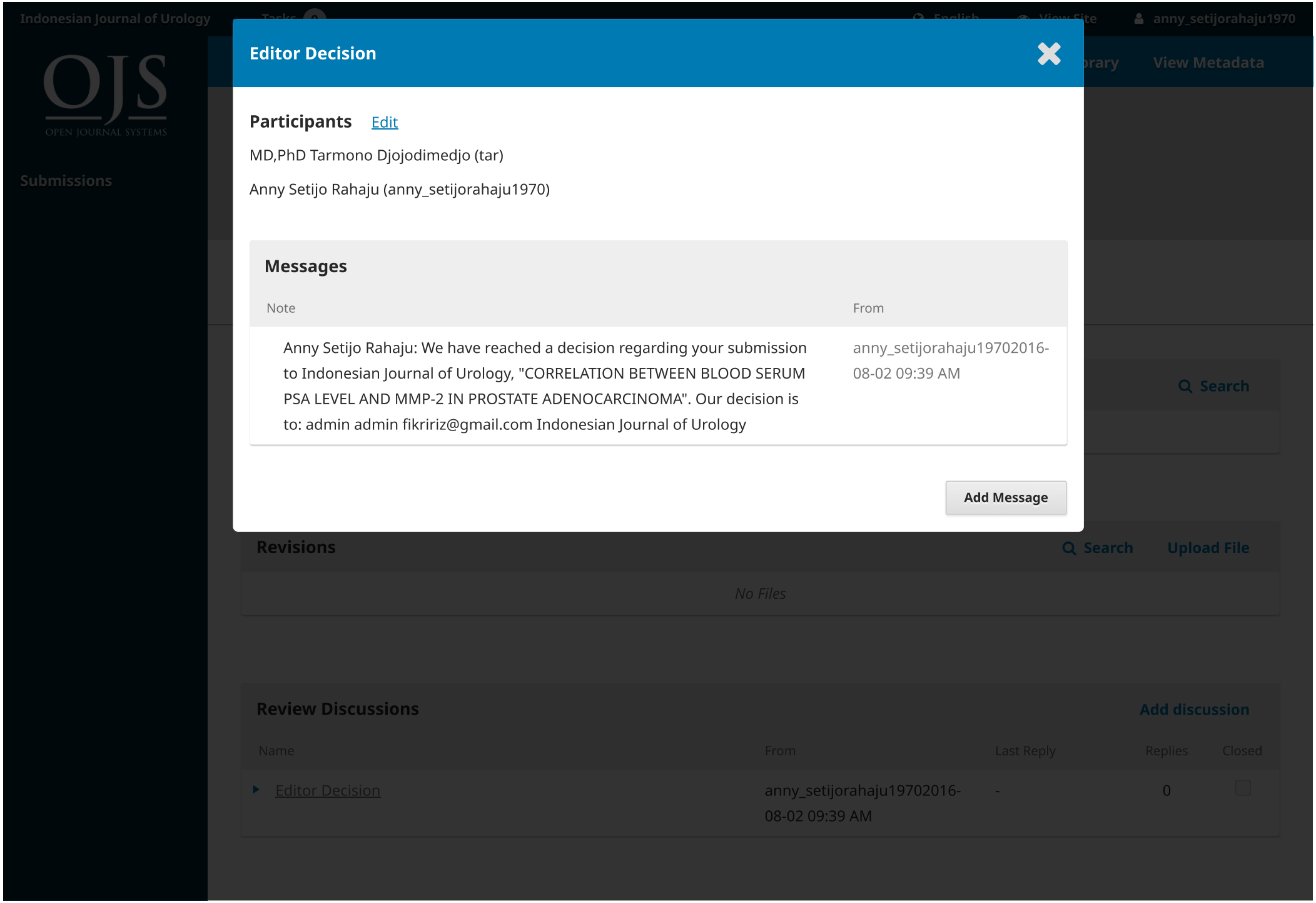
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Abstract *

Objective: This study aims to prove the correlation between Prostate Specific Antigen (PSA) blood level and Matrix Metalloproteinase-2 (MMP-2) expression in patients with prostate adenocarcinoma. **Material & method:** Prostate cancer patients' data from January 2009 to May 2012 were collected at the Department of Pathology, Soetomo General Hospital Surabaya. Data collected included patient medical documents, PSA blood examination, and histopathological examination. Histopathology slides and paraffin blocks of needle biopsies, Transurethral Resection of Prostate (TURP) and radical prostatectomy of prostate cancer patients werere-read, then the samples that met the inclusion criteria were stained by immunohistochemistry using antibodies MMP-2. **Results:** Data collection was done to obtain data

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KORELASI ANTARA KADAR PSA SERUM DARAH DENGAN MMP-2 PADA ADENOKARSINOMA PROSTAT

Anny Setijo Rahaju*, Aniek Meidi*, Gondo Mastutik*, Sjahjenny Mustokoweni*, Arifa Mustika**

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ABSTRAK

Latar Belakang

Kanker prostat merupakan keganasan tersering dan penyebab kematian ke 2 dari semua keganasan pada pria. PSA darah merupakan *tumor marker* yang sering digunakan untuk skrening, karena dapat meningkat pada kanker prostat terutama jenis adenokarsinoma Prostat. Invasi dan metastasis yang terjadi pada adenokarsinoma prostat dapat dinilai dari ekspresi MMP-2 pada sel tumor.

Tujuan

Penelitian ini bertujuan untuk membuktikan hubungan antara kadar PSA darah dengan Ekspresi MMP-2 pada penderita Adenokarsinoma Prostat

Bahan dan Cara

Penelitian ini mengumpulkan data arsip penderita kanker Prostat yang diagnosisnya ditegakkan secara histopatologik adenokarsinoma prostat di Departemen / SMF / Instalasi Patologi Anatomi RSUD Dr. Soetomo mulai Januari 2009 – Mei 2012. Pengumpulan dokumen medik penderita, data pemeriksaan PSA darah serta data pemeriksaan Histopatologi. Slide Histopatologi dan blok parafin hasil biopsi jarum, TURP dan Radikal Prostatectomy penderita kanker Prostat dibaca ulang, kemudian sample memenuhi kriteria inklusi dipulas secara Imunohistokimia dengan menggunakan antibodi MMP-2. pada Hasil diperoleh dengan melakukan uji analitik dengan Korelasi dari Spearman, dengan membandingkan PSA darah penderita dengan Ekspresi MMP-2 pada sel tumor.

Hasil

Pengumpulan data yang dilakukan memperoleh data sample Penderita kanker Prostat pada tahun 2009 sd 2012 sebanyak 22 orang, yang terjadi antara usia 52 - 91 tahun. Adenokarsinoma prostat terbanyak terjadi pada usia 70-79 yaitu 8 orang , dengan rerata pada usia 68 tahun. Nilai PSA yang didapatkan pada dokumen medik antara 8.6 - 594.41 ng/ml.

Semua sample menunjukkan Ekspresi MMP-2 positif pada sitoplasma dan membran sel tumor, dengan prosentase sebanyak 30-70% dan >70 % dan Intensitas yang bervariasi mulai kuning terang sampai dengan coklat. Uji Spearman yang dilakukan pada penelitian ini diperoleh hasil korelasi yang positif (*1-tailed*) (koefisien korelasi (r) 0.431 ,$p<0.05$) antara kadar PSA darah dan ekspresi MMP-2 pada penderita adenokarsinoma prostat.

Kesimpulan

Terdapat korelasi positif antara kadar PSA darah dengan ekspresi MMP-2 pada Adenokarsinoma Prostat. serta peningkatan PSA darah dapat digunakan untuk memprediksi kerusakan ECM pada Adenokarsinoma prostat yang disebabkan MMP-2

Kata Kunci : PSA, MMP-2, Adenokarsinoma Prostat

Pendahuluan

Kanker Prostat merupakan keganasan terbanyak ke-6 dari semua jenis keganasan didunia dan menjadi penyebab kematian kedua akibat kanker pada pria yang disebabkan karena kejadian metastasis. Di Amerika Serikat, Kanker Prostat berjumlah sekitar 29% dari kejadian semua kanker dan sebanyak 10%menjadi penyebab kematian.

Faktor yang ikut berperan untuk aplikasi klinis penderita kanker Prostat, antara lain : kadar Prostate Spesific Antigen serum, *Gleason grade*, stadium tumor, dan tepi operasi. Faktor-faktor tersebut banyak diteliti untuk pengembangan petanda prognostik molekuler pada kanker Prostat. Beberapa literatur menyatakan sel tumor ganas menghasilkan beberapa matriks, yang dapat mendegradasi Extracelluler Matrikx /ECM, antara lain Matrix Metalloproteinase (MMP) family yang berperan dalam invasi dan metastase pada keganasan.

PSA dihasilkan oleh sel epitel luminal kelenjar Prostat yangberupa duktal dan asinar, kemudian disekresikan dalam lumen kelenjar dan dikeluarkan bersama cairan semen di dalam vesikula seminalis. Pada kanker Prostat(Adenokarsinoma) terjadi perubahan pada sel epitel luminal yang dapat menembus sel basal serta terjadi kerusakan pada sel sel basal. Perubahan pada sel epitel Luminal dan kerusakan pada sel Basal menyebabkan PSA yang dihasilkan keluar dari lumen dan masuk dalam sirkulasi darah, sehingga terjadi peningkatan konsentrasi PSA dalam darah. Peningkatan tersebut dapat dideteksi dalam darah dan digunakan untuk skrening dan evaluasi pasca terapi kanker Prostat.

Adenokarsinoma merupakan jenis kanker prostat yang terbanyak ditemukan, dan pada keganasan tersebut terjadi ketidak seimbangan MMP dan Tissue Inhibitor Metalloproteinase (TIMP), yang menyebabkan invasi ke jaringan sekitar dan kejadian metastasis, baik limfogen maupun hematogen. MMP-2 merupakan anggota MMP family yang mempunyai komposisi dan fungsi khusus. MMP-2 (gelatinase A) dalam fungsi invasi dan metastasis, mendegradasi kolagen I dan IV. Invasi dan metastasis yang terjadi pada adenokarsinoma prostat dapat dinilai dari ekspresi MMP-2 pada sel tumor.

Penelitian ini bertujuan untuk membuktikan hubungan kadar PSA serum darah dengan MMP-2 pada Adenokarsinoma Prostat, karena penelitian tentang hubungan kadar PSA serum darah dengan ekspresi MMP-2 pada Adenokarsinoma Prostat masih jarang.

Bahan dan Cara

Penelitian ini merupakan penelitian observasional analitik dengan pendekatan *cross-sectional yang* dilakukan dengan mengumpulkan data arsip penderita kanker Prostat yang diagnosisnya ditegakkan secara histopatologik adenokarsinoma prostat di Departemen / SMF / Instalasi Patologi Anatomi RSUD Dr. Soetomo mulai Januari 2009 – Mei 2012. Data yang dikumpulkan berupa dokumen medik penderita, data pemeriksaan PSA darah serta data pemeriksaan Histopatologi. Slide Histopatologi dan blok parafin hasil biopsi jarum, TURP dan Radikal Prostatectomy penderita kanker Prostat dikumpulkan, kemudian dilakukan pembacaan ulang pada kasus-kasus tersebut. Sample yang diambil adalah penderita yang memenuhi kriteria inklusi dilakukan pulasan Imunohistokimia dengan menggunakan antibodi MMP-2 pada blok yang memenuhi syarat. Hasil diperoleh dengan melakukan uji analitik dengan Korelasi dari Spearman, dengan membandingkan PSA darah penderita dengan Ekspresi MMP-2 pada sel tumor. Penelitian dilakukan di Laboratorium Patologi Anatomi Fakultas Kedokteran Universitas Airlangga Surabaya pada bulan Mei 2015 sampai dengan Agustus 2015.

PSA

Data diperoleh dari dokumen medik. Penderita yang tidak didapatkan data pemeriksaan PSA dikeluarkan dari sampel penelitian. Pemeriksaan kadar PSA serum darah dilakukan dengan metode ELISA.

MMP-2

Pulasan IHK pada blok parafin penderita dengan diagnosis adenokarsinoma prostat, menggunakan antibodi MMP-2. Penilaian ekspresi MMP-2 dilakukan dengan menilai ekspresi pada sitoplasma atau membran sel tumor dengan penilaian intensitas pewarnaan dan persentase sel tumor yang tercat. Pemberian score intensitas : 0= bila sel tumor tidak terwarnai; 1=bila kuning terang; 2 = bila kuning kecoklatan dan 3 = bila coklat, sedangkan prosentase jumlah sel dikalikan. Penentuan Derajat Ekspresi sebagai berikut : 0 (negatif) bila score 0; 1 + bila score 1-3; **2+** bila score 4-6; **3+** bila score 7-9.

Analisis Data

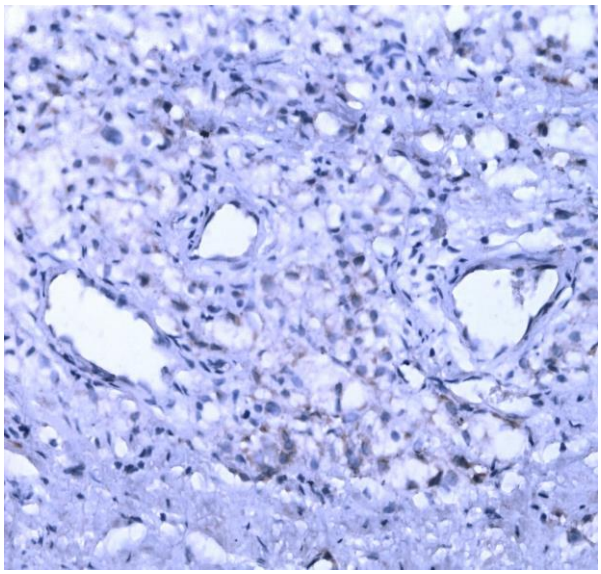
Data PSA dan ekspresi MMP-2 yang diperoleh diuji menggunakan uji korelasi dari *spearman' rho, dengan hasil* bermakna jika nilai p<0,05.

Hasil

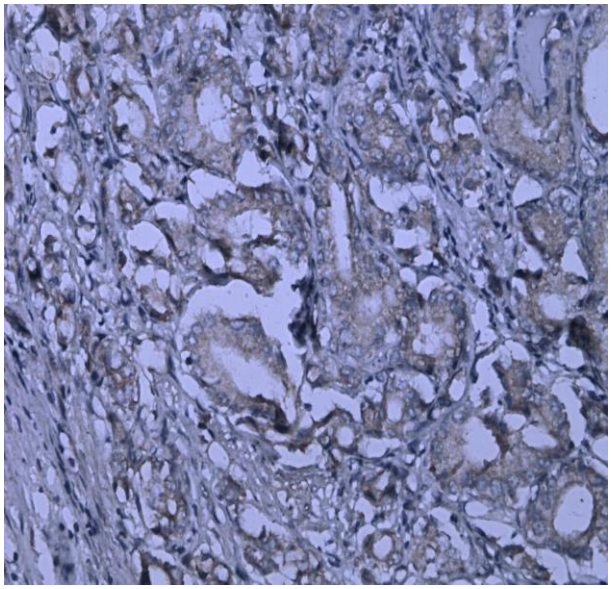
Pengumpulan data yang dilakukan memperoleh data sample Penderita kanker Prostat pada tahun 2009 sd 2012 sebanyak 22 orang, yang terjadi antara usia 52 - 91 tahun. Adenokarsinoma prostat terbanyak terjadi pada usia 70-79 yaitu 8 orang , dengan rerata pada usia 68 tahun. Nilai PSA yang didapatkan pada dokumen medik antara 8.6 - 594.41 ng/ml.

Semua sample menunjukkan Ekspresi MMP-2 positif pada sitoplasma dan membran sel tumor, dengan prosentase sebanyak 30-70% dan >70 % dan Intensitas yang bervariasi mulai kuning terang sampai dengan coklat.

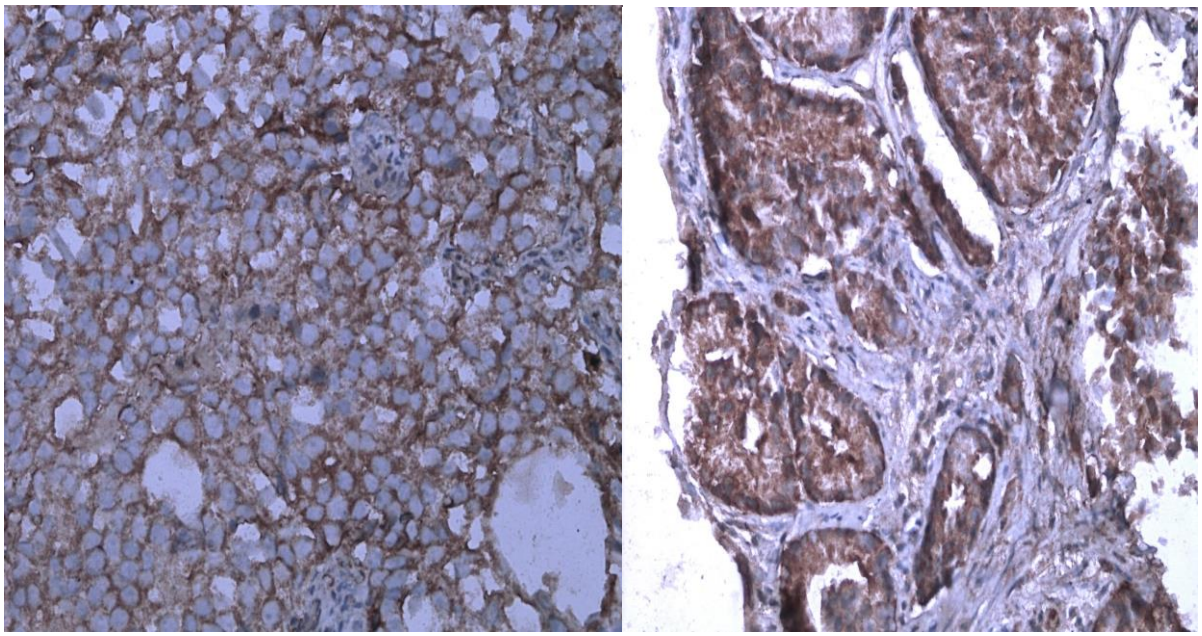
Kemudian Uji Spearman yang dilakukan pada penelitian ini diperoleh hasil korelasi yang positif (*1-tailed*) (koefisien korelasi (r) 0.431 ,p<0.05) antara kadar PSA darah dan ekspresi MMP-2 pada penderita adenokarsinoma prostat.



Gambar. 1 Sediaan T. 3045/12 Persentase >70%(3+) dan Intensitas 1 MMP-2 Intensitas 1 Score +



Gambar 2. Sediaan T. 1662/10 Persentase >70%(3+) dan Intensitas 2



Gambar 3. Sediaan T. 3606/11 dan 6324/10 Persentase >70%(3+) dan Intensitas 3

Tabel 1. Ekspresi MMP-2 pada Adenokarsinoma Prostat

Skor ekspresi MMP-2	%	I	Skor
0	0	0	0
1	0	13	13
2	4	5	5
3	18	4	4
Total	22	22	22

Pembahasan

Nilai PSA darah pada sample penelitian diperoleh antara 8.6 - 594.41 ng/ml, menunjukkan peningkatan kadar PSA serum. Beberapa literatur menyebutkan normal adalah <4 ng/ml (Murray, 2010). Hai itu menunjukkan adanya peningkatan kadar PSA darah bila dibanding normal.

Prostat merupakan organ retro peritoneal yang mengelilingi leherbuli dan uretra, berupa kelenjar berbentuk seperti buah pir. Kelenjar Prostat normal terdiri dua lapis sel, yaitu sel epitel luminal dan sel Basal. Sel sekretorik/Luminal berfungsi menghasilkan cairan seminalis berupa serin Protease (*prostate spesific antigen /*PSA). (Epstein,2004; Rosai J., 2011) Kanker Prostat terbanyak berupa Adenokarsinoma, merupakan tumor ganas invasif yang berasal dari sel epitel luminal. Pada Adenokarsinoma terjadi perubahan pada sel epitel luminal yang dapat menembus sel basal serta terjadi kerusakan pada sel sel basal. Perubahan pada sel epitel Luminal dan kerusakan pada sel Basal menyebabkan PSA yang dihasilkan keluar dari lumen dan masuk dalam sirkulasi darah, sehingga terjadi peningkatan konsentrasi PSA dalam darah. Peningkatan tersebut dapat dideteksi dalam darah dan digunakan untuk skrening dan evaluasi pasca terapi kanker Prostat serta indikasi untuk biopsi pada penderita . PSA juga merupakan marker yang sering digunakan untuk menegakkan diagnosis kanker Prostat (Epstein,2004; Rosai J., 2011; Brosman, 2015)

Murray, pada tahun 2009 juga menyatakan nilai PSA darah berhubungan positif dengan jumlah sel epitel ganas yang tercat dengan pulasan IHK dengan antibodi PSA. Apabila jumlah sel epitel ganas meningkat maka nilai PSA darah jugameningkat. Hal tersebut menunjukkan semakin banyak sel ganas yang merusak barrier akan menyebabkan semakin banyakkadar PSA yang terdeteksi dalam sirkulasi. (Murray,2009)

Proses gangguan integritas sel menyebabkan dilepaskannya PSA dalam sirkulasi, gangguan integrasi ini juga terjadi pada hiperplasi, inflamasi dan tumor. Nilai PSA pada jaringan Prostat jinak : 0.5 ± 0.4 ng/ml, pada BPH : 0.31 ± 0.25 ng/ml, sehingga sampai saat ini belum ada nilai pasti pada kanker. (Brosman, 2015)

Zivcovic mendapatkan hasil kadar 4.0 - 10.0 ng/ml pada Benign hyperplasia, Prostatitis dan kanker prostat. Sedangkan Murray melakukan penelitian dengan mengukur berat jaringan prostat, memberikan hasil tiap gram jaringan kanker prostat dapat meningkatkan PSA sekitar 2.3 ng/ml, jaringan prostat hiperplastik 10 kali lebih rendah

dibanding jaringan kanker. Selain itu juga mendapatkan hasil kadar PSA tertinggi pada lumen kelenjar prostat dan diantara lumen kelenjar dan kapiler pembululuh darah, sel basal pada kelenjar, stroma prostat dan sel endotel kapiler didapatkan barrier yang menghalangi PSA beredar di sirkulasi. Karenanya PSA dapat meningkat secara drastis pada keadaan prostatitis, tetapi dapat kembali normal setelah infeksi teratasi. (Murray, 2009)

Semua sample penelitian ini menunjukkan ekspresi positif pada MMP-2, sesuai Trudel, tahun 2003 memperoleh 70% sel epitel ganas mempunyai ekspresi MMP-2 positif , karena terjadi degradasi ECM oleh MMP-2 .

Adanya korelasi positif antara kadar PSA darah dengan ekspresi MMP-2 pada kanker prostat → peningkatan kadar PSA darah berhubungan dengan peningkatan ekspresi MMP-2 pada kanker prostat. (koefisien korelasi (r) 0.431 ,$p<0.05$)

Sel ganas menghasilkan matriks yang aktif mendegradasi dengan substrat spesifik yang berbeda yang saling bekerjasama dalam degradasi Extracelluler Matrikx /ECM, yaitu Matrix Metalloproteinase family (MMP family) yang berhubungan dengan invasi dan metastase sel tumor. Metastase tumor ini merupakan penyebab utama kematian pada pasien kanker terutama kanker Prostat (Duffy MJ,2000)

Matrix Metalloproteinase (MMP) atau *matrixin* merupakan kelompok struktur *endopeptidase* bebas yang mengandung *zinc*, bekerja sama dengan enzim proteolisis lain seperti *cysteine proteinases, aspartic proteinases* dan *serine proteinase*, yang berperan dalam degradasi matriks ekstraselular (ECM). (Duffy MJ,2000, Verma RP &Hansch C,2007)

MMP disekresi berupa proenzym kemudian diaktifkan oleh adanya celah proteolitik, dan proses ini dapat dihambat oleh *Tissue Inhibitor Metalloproteinase* (TIMP) agar tidak terjadi degradasi. Ketidakseimbangan antara MMP dan TIMP merupakan salah satu penyebab invasi dan metastasis yang terjadi pada tumor ganas.

Degradasi oleh MMP pada proses keganasan, terjadi melalui beberapa tahap, antara lain : 1)membantu membentuk microenvironment melalui pelepasan Growth factor matriks ekstraseluler; 2) Membantu proses angiogenesis tumor, dan meningkatkan kemampuan migrasi dan invasi sel tumor; 3) Berperan pada angiogenesis di lokasi metastasis; 4)Berperan dalam kerusakan membran basalis dinding pembuluh darah, memudahkan intravasasi dan ekstravasasi sel tumor; 5)Berperan membentuk microenvirontment baru ditempat metastasis

Adanya korelasi positif antara kadar PSA darah dengan ekspresi MMP-2 pada kanker prostat menunjukkan peningkatan kadar PSA darah berhubungan dengan peningkatan ekspresi MMP-2 pada kanker prostat. (koefisien korelasi (r) 0.431 ,$p<0.05$) Kadar PSA yang meningkat dalam darah menunjukkan adanya kerusakan barrier yang disebabkan invasi melalui degradasi kolagen tipe I dan IV, serta berbagai kerusakan yang ditimbulkan oleh MMP-2.

Menurut Amalinei, Caruntu dan Balan (2007) berdasarkan spesifitas substrat, persamaan rangkaian dan organisasi domain maka MMP dibagi menjadi 6 grup, yaitu :

Gelatinase (MMP-2, MMP-9); *matrilysins*, (MMP-7, MMP-26)*; collagenases*, (MMP-1, MMP-8, MMP-13)*;stromelysin*, (MMP-3, MMP-10, MMP-11); *membran-type* MMP (MT-MMP→MMP-14, MMP-15, MMP-17,dll); MMP lainnya(MMP-12, MMP-19, dll)

MMP jenis gelatinase (MMP-2 dan MMP-9), memegang peranan penting karena mampu mendegradasi kolagen tipe IV, V, VII, X, XI, XIV, gelatin, elastin proteoglycan core protein, myelin basic protein, fibronektin, fibrilin-1, precursor TNF-α dan IL-1b (Stancovic,2010) MMP-2 mampu memecah kolagen tipe I yang merupakan komponen utama yang membentuk struktur molekul stroma dan memecah kolagen tipe IV merupakan protein penyusun membran basal dan matriks ekstra seluler terbanyak, yang sangat berperan dalam proses invasi. (Stancovic,2010) Begitu juga Murray pada tahun 2009 menyatakan Ekspresi MMP-2 pada sel ganas berperan dalam penyebaran melalui invasi dan metastasis.

Ekspresi MMP-2(gelatinase A) pada beberapa tumor ganas telah banyak diteliti, hal ini berkaitan dengan nilai prognostik. Penelitian tentang MMP-2 ini juga mulai diteliti pada kanker(adenokarsinoma) prostat.

Kesimpulan dan Saran

Kesimpulan

1. Terdapat korelasi positif antara kadar PSA darah dengan ekspresi MMP-2 pada Adenokarsinoma Prostat
2. Peningkatan PSA darah dapat digunakan untuk memprediksi kerusakan ECM pada Adenokarsinoma prostat yang disebabkan MMP-2

Saran

1. Dilakukan penelitian lanjutan dengan sampel yang sesuai dengan populasi
2. Kriteria inklusi tentang bone scan dihilangkan
3. Pemeriksaan kadar PSA sebelum dan sesudah tindakan, kemudian ditentukan *cut off* nya
4. Ditambahkan kelompok sample penderita non Neoplasia (BPH dan atau Prostatitis)

Artikel Submission

KORELASI ANTARA KADAR PSA SERUM DARAH DENGAN MMP-2 PADA ADENOKARSINOMA PROSTAT

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ABSTRAK

Kanker prostat merupakan keganasan tersering dan penyebab kematian kedua dari semua keganasan pada pria.[1,2,3] PSA darah merupakan *tumor marker* yang sering digunakan untuk skrening, karena dapat meningkat pada kanker prostat terutama jenis adenokarsinoma Prostat. Invasi dan metastasis yang terjadi pada adenokarsinoma prostat dapat dinilai dari ekspresi MMP-2 pada sel tumor. Penelitian ini bertujuan untuk membuktikan hubungan antara kadar PSA darah dengan Ekspresi MMP-2 pada penderita Adenokarsinoma Prostat. Data arsip penderita kanker Prostat dikumpulkan di Departemen / SMF / Instalasi Patologi Anatomi RSUD Dr. Soetomo mulai Januari 2009-Mei 2012. Pengumpulan data meliputi dokumen medik penderita, data pemeriksaan PSA darah, dan data pemeriksaan Histopatologi. Slide Histopatologi dan blok parafin hasil biopsi jarum, TURP dan Radikal Prostatectomy penderita kanker Prostat dibaca ulang, kemudian sampel memenuhi kriteria inklusi dipulas secara Imunohistokimia dengan menggunakan antibodi MMP-2. Pengumpulan data yang dilakukan memperoleh data sampel Penderita kanker Prostat pada tahun 2009 sampai 2012 sebanyak 22 orang, yang terjadi antara usia 52 - 91 tahun. Adenokarsinoma prostat terbanyak terjadi pada usia 70-79 yaitu 8 orang , dengan rerata pada usia 68 tahun. Nilai PSA yang didapatkan pada dokumen medik antara 8.6 - 594.41 ng/ml. Uji Spearman yang dilakukan pada penelitian ini diperoleh hasil korelasi yang positif (*1-tailed*) (koefisien korelasi (r) 0.431 ,$p<0.05$) antara kadar PSA darah dan ekspresi MMP-2 pada penderita adenokarsinoma prostat. Terdapat korelasi positif antara kadar PSA darah dengan ekspresi MMP-2 pada Adenokarsinoma Prostat.

Kata Kunci : PSA, MMP-2, Adenokarsinoma Prostat

CORRELATION BETWEEN BLOOD SERUM PSA LEVEL AND MMP-2 IN PROSTATE ADENOCARCINOMA

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ABSTRACT

Prostate cancer is the most common malignancy and the second leading cause of death of all malignancies in men. Blood PSA is a tumor marker that is often used for screening, because its level may elevate in prostate cancer, especially prostate adenocarcinoma. Invasion and metastasis that occurs in prostate adenocarcinoma can be assessed from MMP-2 expression in tumor cells. This study aims to prove the correlation between PSA blood level and MMP-2 expression in patients with prostate adenocarcinoma. Prostate cancer patients' data from January 2009 to May 2012 were collected at the Department of Pathology, Dr. Soetomo Hospital. Data collected included patient medical documents, PSA blood examination, and histopathological examination. Histopathology slides and paraffin blocks of needle biopsies, TURP and radical prostatectomy of prostate cancer patients were re-read, then the samples that met the inclusion criteria were stained by immunohistochemistry using antibodies MMP-2. Data collection was done to obtain data samples of prostate cancer patients in 2009 to 2012 comprising as many as 22 patients between the ages of 52-91 years. Prostate adenocarcinoma in age of 70-79 was found in 8 patients, with a mean age of 68 years. PSA values obtained from medical documents were between 8.6 - 594.41 ng/ml. Spearman's test performed in this study showed a positive correlation (one-tailed) (correlation coefficient (r) 0431, $p < 0.05$) between blood PSA level and MMP-2 expression in patients with prostate adenocarcinoma. Blood PSA level correlates positively with MMP-2 expression in prostate adenocarcinoma.

Keywords: PSA, MMP-2, prostate adenocarcinoma

INTRODUCTION

Prostate cancer was a malignancy of the sixth most-common of all types of malignancies in the world, and becomes the second leading cause of death from cancer in men caused by the incidence of metastasis.[1,2] The incidence of prostate cancer in the United States amounted to about 29% of the incidence of all cancers and 10% of the causes of death.[2,3]

There are factors contributing to the clinical application of prostate cancer, among others, are the level of Prostate Specific Antigen (PSA) in serum, Gleason grade, tumor stage, and operation edge.[4] These factors was studied for the development of molecular prognostic markers in prostate cancer. Some literature suggests that malignant tumor cells produce some matrix that can degrade extracellular matrix (ECM), such as Matrix Metalloproteinase (MMP) family that plays a role in the invasion and metastasis of malignancy.[5]

PSA is generated by the luminal epithelial cells of the prostate gland, primarily in the ductal and acinar regions. It is then released into the gland's lumen and expelled with semen through the seminal vesicles. In prostate cancer (adenocarcinoma) changes in luminal epithelial cells can penetrate and damage basal cells. Changes in luminal epithelial cells and damage in basal cells cause PSA out of the lumen and come into the blood circulation, resulting in increased concentration of PSA in the blood. The increase can be detected in the blood and used for post-therapy screening and evaluation of prostate cancer.[1,2,6]

Adenocarcinoma is a type of prostate cancer that is most commonly found, and in such malignancy there is an imbalance between MMP and Tissue Inhibitor Metalloproteinase (TIMP), which led the invasion into the surrounding tissue and the incidence of metastasis, both lymphogenic and hematogenous.[7,8,9] MMP-2 is a member of the MMP family with a unique structure and function. Known as gelatinase A, MMP-2 plays a role in invasion and metastasis by degrading collagen IV. The expression of MMP-2 in tumor cells can be used to assess invasion and metastasis in prostate adenocarcinoma.[11]

OBJECTIVE

The aim of this study was to prove the correlation between blood serum PSA level and MMP-2 in prostate adenocarcinoma, since studies on the correlation between blood serum PSA levels and MMP-2 expression in prostate adenocarcinoma is rare.

METHODS

This study was an observational analytic study with cross-sectional approach conducted by collecting data from the archive on prostate cancer patients whose diagnosis was established histopathologically as adenocarcinoma of the prostate in the Department of Pathology, Dr. Soetomo Hospital, from January 2009 to May 2012. Data collected were in the form of medical documents of the patients, PSA blood examination and histopathological examination data. Histopathology slides and paraffin blocks of needle biopsies, TURP and Radical Prostatectomy from prostate cancer patients were collected, and then re-reading was done to those cases. Samples taken were patients who had data on blood serum PSA examination by ELISA and met the inclusion criteria. Immunohistochemical staining was done by using MMP-2 antibodies to eligible blocks. Results were obtained by conducting analytical testing with Spearman's correlation by comparing the patients' blood PSA with MMP-2 expression in tumor cells. The study was conducted at the Laboratory of Pathology, Faculty of Medicine, Airlangga University, from May to August 2015.

Immunohistochemical staining on paraffin blocks of patients with a diagnosis of prostate adenocarcinoma was performed using antibodies MMP-2. Assessment of MMP-2 expression was done by assessing the expression in the cytoplasm or tumor cell membrane with staining intensity assessment and the percentage of stained tumor cells. Intensity scores are 0 = tumor cells not stained; 1 = light yellow; 2 = brownish yellow and 3 = brown, while the percentage of cell number is multiplied. The determination of the degree of expression was follows: 0 (negative) when the score is 0; 1+ = 1-3; 2+ = 4-6; and 3+ = 7-9.[12] Data on PSA and MMP-2 expression was tested using Spearman 'rho correlation test, with significant results if $p < 0.05$.

RESULTS

Data collection was done to obtain data on samples of prostate cancer patients from 2009 to 2012 as many as 22 people in ages of 52-91 years. Prostate adenocarcinoma occurred mostly in the age of 70-79, comprising 8 patients, with a mean age 68 years. PSA values obtained from medical documents were between 8.6 - 594.41 ng/ml.

All samples showed positive MMP-2 expression in the cytoplasm and tumor cells membrane, with the percentage as much as 30-70% and >70%. The intensity varied from light yellow to brown. Then Spearman tests conducted in this study showed a positive correlation (one-tailed) (correlation coefficient (r) 0.431, $p < 0.05$) between blood PSA level and MMP-2 expression in patients with prostate adenocarcinoma.

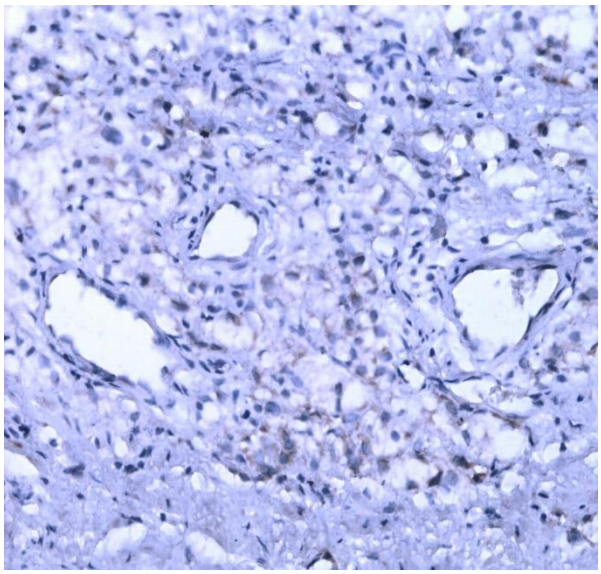

Figure 1. Preparation T. 3045/12, percentage >70%(3+) and intensity 1 MMP-2 intensity 1 score +

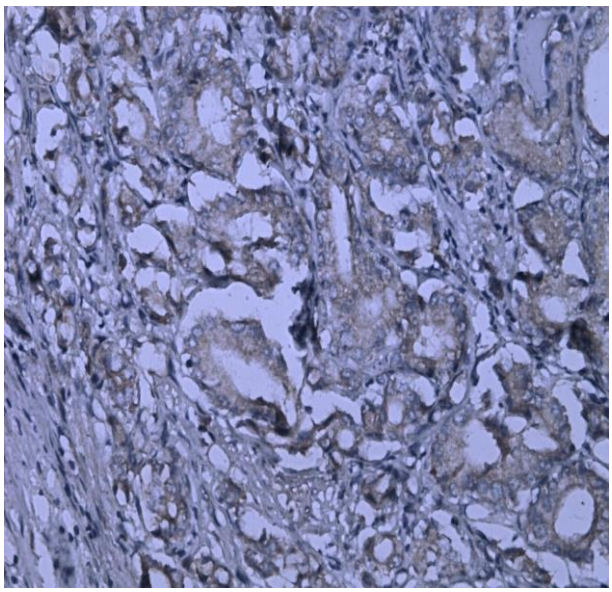

Figure 2. Preparation T. 1662/10 percentage >70%(3+) and intensity 2

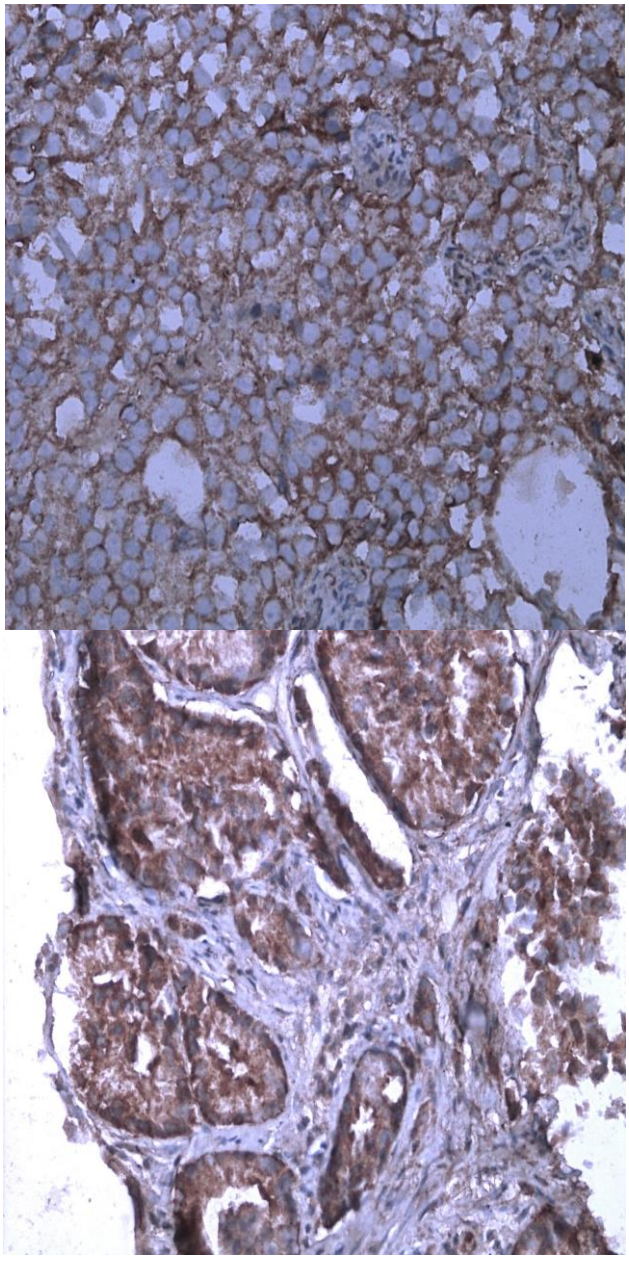

Figure 3. Preparation T. 3606/11 and 6324/10 percentage >70%(3+) and intensity 3

Table 1. MMP-2 expression in prostate adenocarcinoma

MMP-2 expression score	%	I	score
0	0	0	0
1	0	13	13
2	4	5	5
3	18	4	4
Total	22	22	22

Blood PSA value in the sample was between 8.6 - 594.41 ng/ml, showing an increase in serum PSA level. Some literature mentions that the normal level is < 4 ng/ml, showing an increase in blood PSA levels compared to normal.[13,14]

DISCUSSION

The prostate is a retroperitoneal organ that surrounds the bladder neck and urethra, a gland shaped like a pear. Normal prostate gland is composed of two layers of cells: luminal epithelial cells and basal cells. Secretory/luminal cells have a function to produce seminal fluid in the form of serine protease (prostate specific antigen/PSA).[1,2] Prostate cancer is most commonly in the form of adenocarcinoma, which is an invasive malignant tumor derived from luminal epithelial cells. In adenocarcinoma, luminal epithelial cells undergo changes that enable them to invade basal cells, leading to basal cell damage. These alterations in the luminal epithelial cells and the damage to basal cells cause PSA to leak out of the lumen and into the bloodstream, resulting in elevated PSA levels in the blood. The increase can be detected in blood and is used for screening and evaluation of prostate cancer post-treatment as well as indications for biopsy in patients. PSA is also a marker that is often used to diagnose prostate cancer.[1,2,6]

Murray in 2010 also stated that blood PSA value was positively related to the number of malignant epithelial cells stained with immunohistochemical staining with PSA antibody. Increasing number of malignant epithelial cells results in increased blood PSA level, indicating that more malignant cells that damage the barrier will lead to higher levels of PSA detected in the circulation.[14]

The process of cell integrity disruption causes the release of PSA in circulation. This integration disorder also occurs in hyperplasia, inflammation and tumors. PSA value in benign prostate tissue: 0.5 ± 0.4 ng/ml, in BPH: 0:31 ± 0:25 ng/ml, so that up to now there is no definite value in cancer.[6]

Zivkovic in 2004 obtain levels of 4.0 - 10.0 ng/ml in benign hyperplasia, prostatitis and prostate cancer. Murray conducted a study in 2010 by measuring the weight of prostate tissue, giving results that each gram of prostate cancer tissue can increase PSA of approximately 2.3 ng/ml. The PSA level in hyperplastic prostate tissue is ten times lower than in cancerous tissue. Additionally, it was observed that the highest PSA concentration is found in the lumen of the prostate gland. A barrier exists between the gland's lumen, basal cells, prostate stroma, capillary blood vessels, and capillary endothelial cells, which prevents PSA from entering the bloodstream. Therefore, PSA can increase drastically in the state of prostatitis, but can return to normal after the infection resolved.[14]

All samples of this study showed positive expression of MMP-2, according to a study by Trudel (2003), who found that 70% of malignant epithelial cells had positive expression of MMP-2 due to the degradation of ECM by MMP-2.[15] There was a positive correlation between blood PSA levels with MMP-2 expression in prostate cancer, showing that increased blood PSA level is associated with increased MMP-2 expression in prostate cancer (correlation coefficient (r) 0.431, $p < 0.05$).

Malignant cells produce matrix that actively degrades with different specific substrates that act together in the degradation of Extracelluler Matrikx (ECM), that is the Matrix

Metalloproteinase (MMP) family, which is associated with the invasion and metastasis of tumor cells. This tumor metastases is the main cause of death in patients with cancer, particularly prostate cancer.[8,16]

Matrix Metalloproteinase (MMP), or matrixin, is a group of free endopeptidase structure that contain zinc, in cooperation with other proteolysis enzymes, such as cysteine proteinases, aspartic proteinase and serine proteinase, which plays a role in extracellular matrix degradation.[8,9] MMP is secreted in the form of proenzyme, then be activated by the proteolytic gap, and this process can be inhibited by Tissue Inhibitor Metalloproteinase (TIMP) in order to avoid degradation. Imbalance between MMP and TIMP is one of the causes of invasion and metastasis that occurs in malignant tumors.[7,8,9,10] Such imbalance is also an important factor that participates in tumor progression.[17] The expression of MMPs (MMP-2 and MMP-9) is often associated with tumor aggressiveness and overall survival, and it is also often used as a marker of malignancy.[18]

Degradation by MMP in malignancy process is taking place through several stages, including: 1) assisting the formation of a microenvironment through the release of extracellular matrix growth factor; 2) assisting the process of tumor angiogenesis, and enhancing the ability of the migration and invasion of tumor cells; 3) playing a role in angiogenesis at the site of metastasis; 4) playing a role in the damage to basal membrane of blood vessel walls, allowing intravasation and extravasation of tumor cells; and 5) playing a role in shaping new microenvirontment at metastasis site.[19]

Positive correlation between blood PSA levels with MMP-2 expression in prostate cancer showed that increased blood PSA level is associated with increased MMP-2 expression in prostate cancer (correlation coefficient (r) 0431, $p < 0.05$). Increased PSA levels in blood indicates barrier damage caused by invasion through the degradation of collagen type IV, as well as damage caused by MMP-2.[20]

According to Amalinei, Caruntu and Balan (2007), based on the substrate specificity, sequence similarity, and domain organization, MMP is divided into 6 groups: gelatinase (MMP-2, MMP-9); matrilysins (MMP-7, MMP-26); collagenases (MMP-1, MMP-8, MMP-13); stromelysin (MMP-3, MMP-10, MMP-11); membrane-type MMP (MT-MMP -> MMP-14, MMP-15, MMP-17, etc.); and other MMPs (MMP-12, MMP-19, etc.).[20]

Gelatinase-type MMP (MMP-2 and MMP-9) plays an important role because it can degrade collagen types IV, V, VII, X, XI, XIV, gelatin, elastin, proteoglycan core proteins, myelin basic protein, fibronectin, fibrillin-1, a precursor TNF-alpha and IL-1b. MMP-2 is able to break down collagen type I, which is the main component that forms the stroma and break down the molecular structure of collagen type IV which is a most protein constituent of basal membrane and the extra cellular matrix, which is instrumental in the invasion process.[7,8,9,10] Similarly, Murray in 2009 found that the expression of MMP-2 plays a role in the spread of malignant cells through invasion and metastasis.[14] MMP-2 expression (gelatinase A) in some malignant tumors has been widely studied. This relates to the prognostic value. Studies on the MMP-2 have also been started in prostate cancer (adenocarcinoma).

CONCLUSION

There are a correlation between blood PSA level and MMP-2 expression in patients with prostate adenocarcinoma. Blood PSA value in the sample was between 8.6 - 594.41 ng/ml, showing an increase in serum PSA level. Blood PSA level correlates positively with MMP-2 expression in prostate adenocarcinoma, and increased blood PSA can be used to predict ECM damage in MMP-2-induced prostate adenocarcinoma.

REFERENCES

1 Epstein, JI, Algaba, F, Allbrook, WC, Bastacky, S, et al. Acinar adenocarcinoma, in WHO classification of tumours, pathology and genetics tumours of the urinary system and male genital organs, Ed. Ebk JN, IARC Press, Lyon. 2004; hh.161- 92.

2 Rosai, J. Male reproductive system. in Rosai and Ackerman's surgical pathology. vol.1, 9th ed, Elsevier, China, 2011; hh. 1361-87.

3 Epstein, JI. The lower urinary tract and male genital system, in Robbins pathologic basic of disease, 8th ed, Saunders, Philadelphia, 2010; hh. 993-1003.

4 Young, RH. Atlas of tumors pathology, tumors of the prostate gland, seminal vesicles, male uretra, and penis, 3rd series, Armed Forces Institute of Pathology, Washington DC, 2000; hh. 111-200.

5 Brehmer B, Biesterfeld S, Jakse G. Expression of matrix metalloproteinases (MMP-2 and -9) and their inhibitors (TIMP-1 and -2) in prostate cancer tissue, Prostate Cancer and Prostatic Diseases 6, 2003; 217–222. doi:10.1038/sj.pcan.4500657. http://emedicine.medscape.com/article/457394-overview

6 Nelson RA, Fingleton B, Rothenberg ML, Matrisian LM, Matrix metalloproteinases: Biologic activity and clinical implications, Journal of clinical Oncology, 2000, 218(5):1135-1149.

7 Duffy MJ, Maguire TM, Hill A, McDermott E, O'Higgins N. Metalloproteinases: role in breast carcinogenesis, invasion and metastasis. Breast cancer res. 2000;2(4):252 - 7.

8 Verma RP &Hansch C, Matrix metalloproteinase (MMPs) : chemical-biological function and (Q) SARs; 2007, Bioorg Med Chem 15(6) : 2223-68.

9 Tero Leinonen, Risto Pirinen, Jan Bohm, et al. Increased expression of matrix metalloproteinase-2(MMP-2) predicts tumour recurrence and unfavourable outcome in non-small cell lung cancer. In Histol Histopathol; 008; 23: 693-700 http://atlasgeneticsoncology.org/Genes/MMP2ID41396ch16q13.html

10 Daniel Kaemmerer, Luisa Peter, Emelie Lupp, et al. Original Article: Comparing of IRS as Immunohistochemical scoring schemes in gastroenteropancreatic neuroendocrine tumors. Int J Clin Exp Pathol ; 2012;5(3):187- 94

11 Stadiana Zivkovic. Original article : Correlation between proatate-specific antigen and histopathological difference of prostate carcinoma. In Arch Oncol; 2004; 12(3); 148-51

12 Nigel P. Murray, Gloria M. Calaf, Leonardo Badinez, et al. P504S expressing circulating prostate cells as a marker for prostate cancer. In Oncology Reports; 2010; 24; 687-92

13 Dominique trudel, Yves fradet, Franc, et al. Significance of mmp-2 expression in prostate cancer. An immunohistochemical study. In Cancer research ; 2003; 63; 8511–15

14 Yixuan Gong, Uma D. Chippada-Venkata, William K. Oh. Reviews: Roles of Matrix metalloproteinase and Their Natural Inhibitors in Prostate Cancer Progression. Cancers; 2014; 6 ; 1298-327

15 B Brehmer, S Biesterfeld, G Jakse. Prostate Cancer and Prostatic Disease: Expression of matrix metalloproteinase (MMP-2 and -9) and their inhibitors (TIMP-1 and -2) in prostate cancer tissue. 2003; 6; 217-22.
16 Romano Oguic, Vladimir Mozetic, Eleonora Cini Tesar, et al. Research article: Matrix metalloproteinase 2 and 9 Immunoexpression in Prostate Carcinoma at the positive Margin of Radical Prostatectomy Specimen. In Hindawi Publishing Corporation Pathology Research International ; 2014; Article ID 262195; 8. http://www.ncbi.nlm.nih.gov/gene/4313
17 Amalinei C, Caruntu ID, Balan RA. Biology of metalloproteinases, Romanian Journal of Morphology and Embryology, 2007; 48 (4) : 323-34.
18 Stankovic S, Konjevic G, Gopcevic K, Jovic V, Inic M, Jurisic V. Activity of MMP-2 and MMP-9 in sera of breast cancer patients. Pathology - Research and Practice. 2010;206(4):241-7.

Artikel After Revisi 1

KORELASI ANTARA KADAR PSA SERUM DARAH DENGAN MMP-2 PADA ADENOKARSINOMA PROSTAT

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ABSTRAK

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Kata Kunci : PSA, MMP-2, Adenokarsinoma Prostat

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INTRODUCTION

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METHODS

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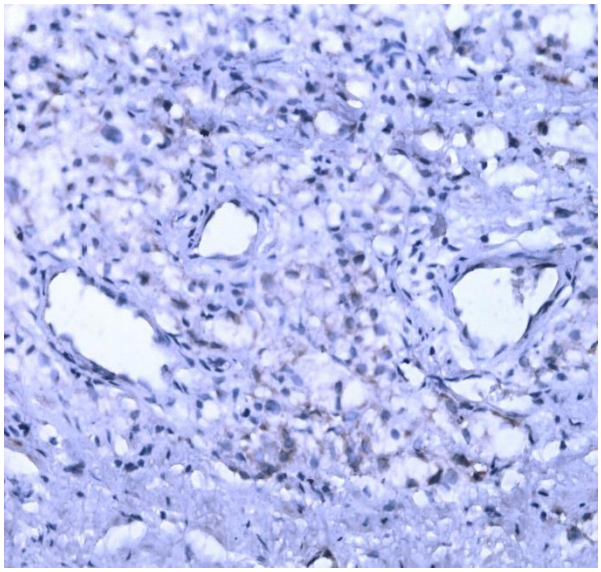


Figure 1. Preparation T. 3045/12, percentage >70%(3+) and intensity 1 MMP-2 intensity 1 score +

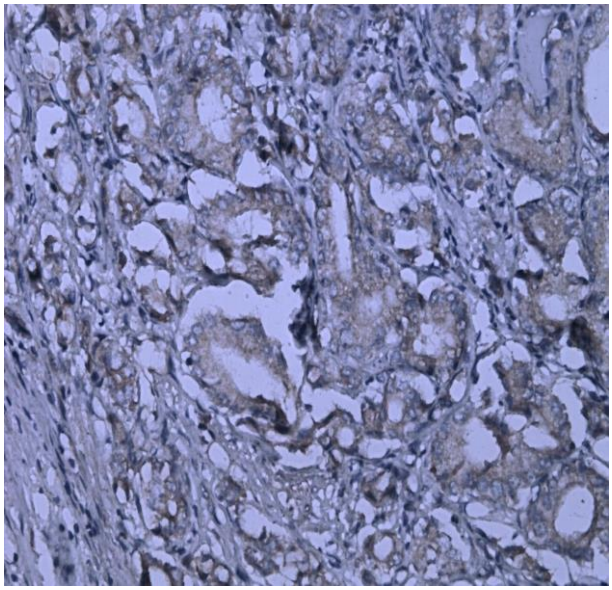
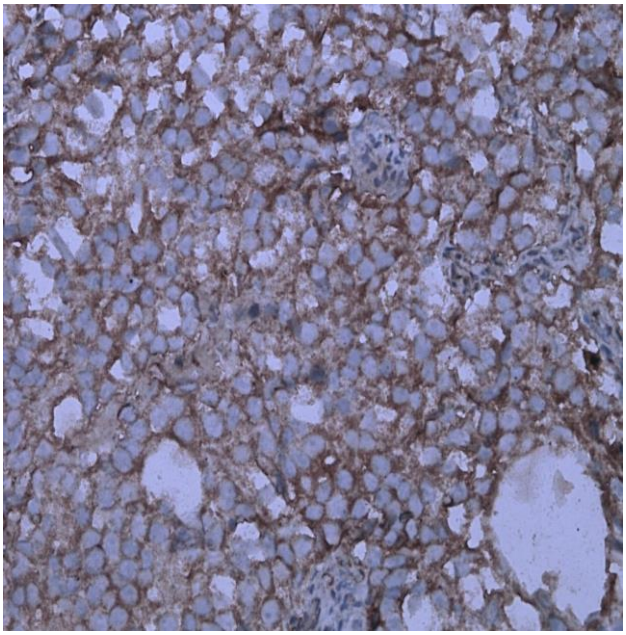


Figure 2. Preparation T. 1662/10 percentage >70%(3+) and intensity 2



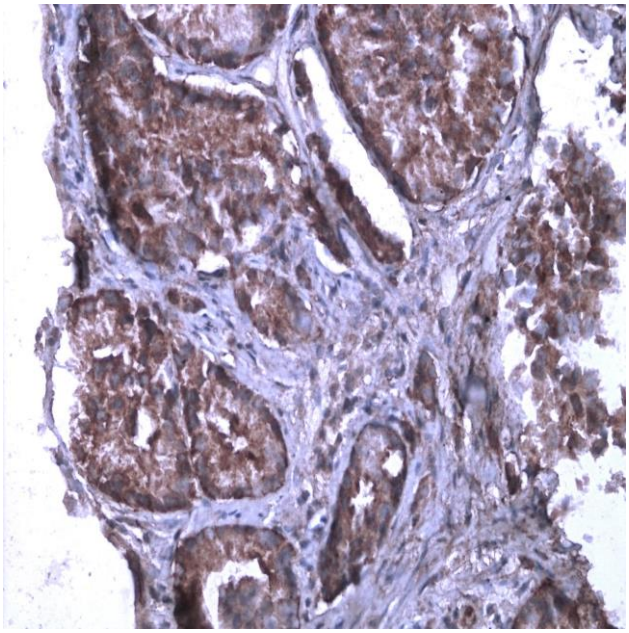


Figure 3. Preparation T. 3606/11 and 6324/10 percentage >70%(3+) and intensity 3

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MMP-2 expression score	%	I	score
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Blood PSA value in the sample was between 8.6 - 594.41 ng/ml, showing an increase in serum PSA level. Some literature mentions that the normal level is < 4 ng/ml, showing an increase in blood PSA levels compared to normal.[13,14]

DISCUSSION

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All samples of this study showed positive expression of MMP-2, according to a study by Trudel (2003), who found that 70% of malignant epithelial cells had positive expression of MMP-2 due to the degradation of ECM by MMP-2.[15] There was a positive correlation between blood PSA levels with MMP-2 expression in prostate cancer, showing that increased blood PSA level is associated with increased MMP-2 expression in prostate cancer (correlation coefficient (r) 0.431, $p < 0.05$).

Malignant cells produce matrix that actively degrades with different specific substrates that act together in the degradation of Extracelluler Matrikx (ECM), that is the Matrix Metalloproteinase (MMP) family, which is associated with the invasion and metastasis of tumor cells. This tumor metastases is the main cause of death in patients with cancer, particularly prostate cancer.[8,16]

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Positive correlation between blood PSA levels with MMP-2 expression in prostate cancer showed that increased blood PSA level is associated with increased MMP-2 expression in prostate cancer (correlation coefficient (r) 0431, $p < 0.05$). Increased PSA levels in blood indicates barrier damage caused by invasion through the degradation of collagen type IV, as well as damage caused by MMP-2.[20]

According to Amalinei, Caruntu and Balan (2007), based on the substrate specificity, sequence similarity, and domain organization, MMP is divided into 6 groups: gelatinase (MMP-2, MMP-9); matrilysins (MMP-7, MMP-26); collagenases (MMP-1, MMP-8, MMP-13); stromelysin (MMP-3, MMP-10, MMP-11); membrane-type MMP (MT-MMP -> MMP-14, MMP-15, MMP-17, etc.); and other MMPs (MMP-12, MMP-19, etc.).[20] In addition, the Gleason score is used to assess the tumor grading. It consists of 5 tiered scores ranging from 6 to 10.

Gelatinase-type MMP (MMP-2 and MMP-9) plays an important role because it can degrade collagen types IV, V, VII, X, XI, XIV, gelatin, elastin, proteoglycan core proteins, myelin basic protein, fibronectin, fibrillin-1, a precursor TNF-alpha and IL-1b. MMP-2 is able to break down collagen type I, which is the main component that forms the stroma and break down the molecular structure of collagen type IV which is a most protein constituent of basal membrane and the extra cellular matrix, which is instrumental in the invasion process.[7,8,9,10] Similarly, Murray in 2009 found that the expression of MMP-2 plays a role in the spread of malignant cells through invasion and metastasis.[14] MMP-2 expression (gelatinase A) in some malignant tumors has been widely studied. This relates to the prognostic value. Studies on the MMP-2 have also been started in prostate cancer (adenocarcinoma).

CONCLUSION

~~There are a correlation between blood PSA level and MMP-2 expression in patients with prostate adenocarcinoma~~. ~~Blood PSA value in the sample was between 8.6 - 594.41 ng/ml, showing an increase in serum PSA level.~~ Blood PSA level correlates positively with MMP-2 expression in prostate adenocarcinoma, and increased blood PSA can be used to predict ECM damage in MMP-2-induced prostate adenocarcinoma.

REFERENCES

1 Epstein, JI, Algaba, F, Allbrook, WC, Bastacky, S, et al. Acinar adenocarcinoma, in WHO classification of tumours, pathology and genetics tumours of the urinary system and male genital organs, Ed. Ebk JN, IARC Press, Lyon. 2004; hh.161- 92.
2 Rosai, J. Male reproductive system. in Rosai and Ackerman's surgical pathology. vol.1, 9th ed, Elsevier, China, 2011; hh. 1361-87.
3 Epstein, JI. The lower urinary tract and male genital system, in Robbins pathologic basic of disease, 8th ed, Saunders, Philadelphia, 2010; hh. 993-1003.
4 Young, RH. Atlas of tumors pathology, tumors of the prostate gland, seminal vesicles, male uretra, and penis, 3rd series, Armed Forces Institute of Pathology, Washington DC, 2000; hh. 111-200.
5 Brehmer B, Biesterfeld S, Jakse G. Expression of matrix metalloproteinases (MMP-2 and -9) and their inhibitors (TIMP-1 and -2) in prostate cancer tissue, Prostate Cancer and Prostatic Diseases 6, 2003; 217–222. doi:10.1038/sj.pcan.4500657. http://emedicine.medscape.com/article/457394-overview
6 Nelson RA, Fingleton B, Rothenberg ML, Matrisian LM, Matrix metalloproteinases: Biologic activity and clinical implications, Journal of clinical Oncology, 2000, 218(5):1135-1149.
7 Duffy MJ, Maguire TM, Hill A, McDermott E, O'Higgins N. Metalloproteinases: role in breast carcinogenesis, invasion and metastasis. Breast cancer res. 2000;2(4):252 - 7.
8 Verma RP &Hansch C, Matrix metalloproteinase (MMPs) : chemical-biological function and (Q) SARs; 2007, Bioorg Med Chem 15(6) : 2223-68.
9 Tero Leinonen, Risto Pirinen, Jan Bohm, et al. Increased expression of matrix metalloproteinase-2(MMP-2) predicts tumour recurrence and unfavourable outcome in non-small cell lung cancer. In Histol Histopathol; 008; 23: 693-700 http://atlasgeneticsoncology.org/Genes/MMP2ID41396ch16q13.html
10 Daniel Kaemmerer, Luisa Peter, Emelie Lupp, et al. Original Article: Comparing of IRS as Immunohistochemical scoring schemes in gastroenteropancreatic neuroendocrine tumors. Int J Clin Exp Pathol ; 2012;5(3):187- 94
11 Stadiana Zivkovic. Original article : Correlation between proatate-specific antigen and histopathological difference of prostate carcinoma. In Arch Oncol; 2004; 12(3); 148-51
12 Nigel P. Murray, Gloria M. Calaf, Leonardo Badinez, et al. P504S expressing circulating prostate cells as a marker for prostate cancer. In Oncology Reports; 2010; 24; 687-92
13 Dominique trudel, Yves fradet, Franc, et al. Significance of mmp-2 expression in prostate cancer. An immunohistochemical study. In Cancer research ; 2003; 63; 8511–15
14 Yixuan Gong, Uma D. Chippada-Venkata, William K. Oh. Reviews: Roles of Matrix metalloproteinase and Their Natural Inhibitors in Prostate Cancer Progression. Cancers; 2014; 6 ; 1298-327
15 B Brehmer, S Biesterfeld, G Jakse. Prostate Cancer and Prostatic Disease: Expression of matrix metalloproteinase (MMP-2 and -9) and their inhibitors (TIMP-1 and -2) in prostate cancer tissue. 2003; 6; 217-22.
16 Romano Oguic, Vladimir Mozetic, Eleonora Cini Tesar, et al. Research article: Matrix metalloproteinase 2 and 9 Immunoexpression in Prostate Carcinoma at the positive Margin of Radical Prostatectomy Specimen. In Hindawi Publishing Corporation Pathology Research International ; 2014; Article ID 262195; 8. http://www.ncbi.nlm.nih.gov/gene/4313
17 Amalinei C, Caruntu ID, Balan RA. Biology of metalloproteinases, Romanian Journal of Morphology and Embryology, 2007; 48 (4) : 323-34.

18 Stankovic S, Konjevic G, Gopcevic K, Jovic V, Inic M, Jurisic V. Activity of MMP-2 and MMP-9 in sera of breast cancer patients. Pathology - Research and Practice. 2010;206(4):241-7.

Artikel After Revisi 2

KORELASI ANTARA KADAR PSA SERUM DARAH DENGAN MMP-2 PADA ADENOKARSINOMA PROSTAT

Anny Setijo Rahaju[1], Aniek Meidi[1], Gondo Mastutik[1], Sjahjenny Mustokoweni[1], Arifa Mustika[2]

[1]Departemen Patologi Anatomi, Fakultas Kedokteran Universitas Airlangga

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ABSTRAK

Kanker prostat merupakan keganasan tersering dan penyebab kematian kedua dari semua keganasan pada pria.[1,2,3] PSA darah merupakan *tumor marker* yang sering digunakan untuk skrening, karena dapat meningkat pada kanker prostat terutama jenis adenokarsinoma Prostat. Invasi dan metastasis yang terjadi pada adenokarsinoma prostat dapat dinilai dari ekspresi MMP-2 pada sel tumor. Penelitian ini bertujuan untuk membuktikan hubungan antara kadar PSA darah dengan Ekspresi MMP-2 pada penderita Adenokarsinoma Prostat. Data arsip penderita kanker Prostat dikumpulkan di Departemen / SMF / Instalasi Patologi Anatomi RSUD Dr. Soetomo mulai Januari 2009-Mei 2012. Pengumpulan data meliputi dokumen medik penderita, data pemeriksaan PSA darah, dan data pemeriksaan Histopatologi. Slide Histopatologi dan blok parafin hasil biopsi jarum, TURP dan Radikal Prostatectomy penderita kanker Prostat dibaca ulang, kemudian sampel memenuhi kriteria inklusi dipulas secara Imunohistokimia dengan menggunakan antibodi MMP-2. Pengumpulan data yang dilakukan memperoleh data sampel Penderita kanker Prostat pada tahun 2009 sampai 2012 sebanyak 22 orang, yang terjadi antara usia 52 - 91 tahun. Adenokarsinoma prostat terbanyak terjadi pada usia 70-79 yaitu 8 orang , dengan rerata pada usia 68 tahun. Nilai PSA yang didapatkan pada dokumen medik antara 8.6 - 594.41 ng/ml. Uji Spearman yang dilakukan pada penelitian ini diperoleh hasil korelasi yang positif (*1-tailed*) (koefisien korelasi (r) 0.431 ,$p<0.05$) antara kadar PSA darah dan ekspresi MMP-2 pada penderita adenokarsinoma prostat. Terdapat korelasi positif antara kadar PSA darah dengan ekspresi MMP-2 pada Adenokarsinoma Prostat.

Kata Kunci : PSA, MMP-2, Adenokarsinoma Prostat

CORRELATION BETWEEN BLOOD SERUM PSA LEVEL AND MMP-2 IN PROSTATE ADENOCARCINOMA

Anny Setijo Rahaju[1], Aniek Meidi[1], Gondo Mastutik[1], Sjahjenny Mustokoweni[1], Arifa Mustika[2]
[1]Department of Anatomic Pathology, [2]Department of Pharmacology
Faculty of Medicine, Airlangga University

ABSTRACT

Prostate cancer is the most common malignancy and the second leading cause of death of all malignancies in men. Blood PSA is a tumor marker that is often used for screening, because its level may elevate in prostate cancer, especially prostate adenocarcinoma. Invasion and metastasis that occurs in prostate adenocarcinoma can be assessed from MMP-2 expression in tumor cells. This study aims to prove the correlation between PSA blood level and MMP-2 expression in patients with prostate adenocarcinoma. Prostate cancer patients' data from January 2009 to May 2012 were collected at the Department of Pathology, Dr. Soetomo Hospital. Data collected included patient medical documents, PSA blood examination, and histopathological examination. Histopathology slides and paraffin blocks of needle biopsies, TURP and radical prostatectomy of prostate cancer patients were re-read, then the samples that met the inclusion criteria were stained by immunohistochemistry using antibodies MMP-2. Data collection was done to obtain data samples of prostate cancer patients in 2009 to 2012 comprising as many as 22 patients between the ages of 52-91 years. Prostate adenocarcinoma in age of 70-79 was found in 8 patients, with a mean age of 68 years. PSA values obtained from medical documents were between 8.6 - 594.41 ng/ml. Spearman's test performed in this study showed a positive correlation (one-tailed) (correlation coefficient (r) 0431, $p < 0.05$) between blood PSA level and MMP-2 expression in patients with prostate adenocarcinoma. Blood PSA level correlates positively with MMP-2 expression in prostate adenocarcinoma.

Keywords: PSA, MMP-2, prostate adenocarcinoma

INTRODUCTION

Prostate cancer ~~was~~ is a malignancy of the sixth most-common of all types of malignancies in the world, and becomes the second leading cause of death from cancer in men caused by the incidence of metastasis.[1,2] The incidence of prostate cancer in the United States amounted to about 29% of the incidence of all cancers and 10% of the causes of death.[2,3]

~~There are~~ Factors contributing to the clinical application of prostate cancer, among others, are the level of Prostate Specific Antigen (PSA) in serum, Gleason grade, tumor stage, and operation edge.[4] These factors ~~was~~ have been studied for the development of molecular prognostic markers in prostate cancer. Some literature suggests that malignant tumor cells produce some matrix that can degrade extracellular matrix (ECM), such as Matrix Metalloproteinase (MMP) family that plays a role in the invasion and metastasis of malignancy.[5]

~~PSA is generated by the luminal epithelial cells of the prostate gland, primarily in the ductal and acinar regions. It is then released into the gland's lumen and expelled with semen through the seminal vesicles.~~ PSA is produced by prostate gland luminal epithelial cells in the form of ductal and acinar, then secreted into the lumen of the gland and excreted along with semen within the seminal vesicles. In prostate cancer (adenocarcinoma) changes in luminal epithelial cells can penetrate and damage basal cells. Changes in luminal epithelial cells and damage in basal cells cause PSA out of the lumen and come into the blood circulation, resulting in increased concentration of PSA in the blood. The increase can be detected in the blood and used for post-therapy screening and evaluation of prostate cancer.[1,2,6]

Adenocarcinoma is a type of prostate cancer that is most commonly found, and in such malignancy there is an imbalance between MMP and Tissue Inhibitor Metalloproteinase (TIMP), which led the invasion into the surrounding tissue and the incidence of metastasis, both lymphogenic and hematogenous.[7,8,9] ~~MMP-2 is a member of the MMP family with a unique structure and function. Known as gelatinase A, MMP-2 plays a role in invasion and metastasis by degrading collagen IV. The expression of MMP-2 in tumor cells can be used to assess invasion and metastasis in prostate adenocarcinoma.~~ MMP-2 is a member of MMP family that has a special composition and function. MMP-2 (gelatinase A), in its function of invasion and metastasis, degrades collagen IV.[10] The invasion and metastasis that occurs in prostate adenocarcinoma can be assessed from the expression of MMP-2 in tumor cells.[11]

OBJECTIVE

The aim of this study was to prove the correlation between blood serum PSA level and MMP-2 in prostate adenocarcinoma, since studies on the correlation between blood serum PSA levels and MMP-2 expression in prostate adenocarcinoma is rare.

METHODS

This study was an observational analytic study with cross-sectional approach conducted by collecting data from the archive on prostate cancer patients whose diagnosis was established histopathologically as adenocarcinoma of the prostate in the Department of Pathology, Dr. Soetomo Hospital, from January 2009 to May 2012. Data collected were in the form of medical documents of the patients, PSA blood examination and histopathological examination data. Histopathology slides and paraffin blocks of needle biopsies, TURP and Radical Prostatectomy from prostate cancer patients were collected, and then re-reading was done to those cases. Samples taken were patients who had data on blood serum PSA examination by ELISA and met the inclusion criteria. Immunohistochemical staining was done by using MMP-2 antibodies to eligible blocks. Results were obtained by conducting analytical testing with Spearman's correlation by comparing the patients' blood PSA with MMP-2 expression in tumor cells. The study was conducted at the Laboratory of Pathology, Faculty of Medicine, Airlangga University, from May to August 2015.

Immunohistochemical staining on paraffin blocks of patients with a diagnosis of prostate adenocarcinoma was performed using antibodies MMP-2. Assessment of MMP-2 expression was done by assessing the expression in the cytoplasm or tumor cell membrane

with staining intensity assessment and the percentage of stained tumor cells. Intensity scores are 0 = tumor cells not stained; 1 = light yellow; 2 = brownish yellow and 3 = brown, while the percentage of cell number is multiplied. The determination of the degree of expression was follows: 0 (negative) when the score is 0; 1+ = 1-3; 2+ = 4-6; and 3+ = 7-9.[12] Data on PSA and MMP-2 expression was tested using Spearman 'rho correlation test, with significant results if $p < 0.05$.

RESULTS

Data collection was done to obtain data on samples of prostate cancer patients from 2009 to 2012 as many as 22 people in ages of 52-91 years. Prostate adenocarcinoma occurred mostly in the age of 70-79, comprising 8 patients, with a mean age 68 years. PSA values obtained from medical documents were between 8.6 - 594.41 ng/ml.

All samples showed positive MMP-2 expression in the cytoplasm and tumor cells membrane, with the percentage as much as 30-70% and >70%. The intensity varied from light yellow to brown. Then Spearman tests conducted in this study showed a positive correlation (one-tailed) (correlation coefficient (r) 0.431, $p < 0.05$) between blood PSA level and MMP-2 expression in patients with prostate adenocarcinoma.

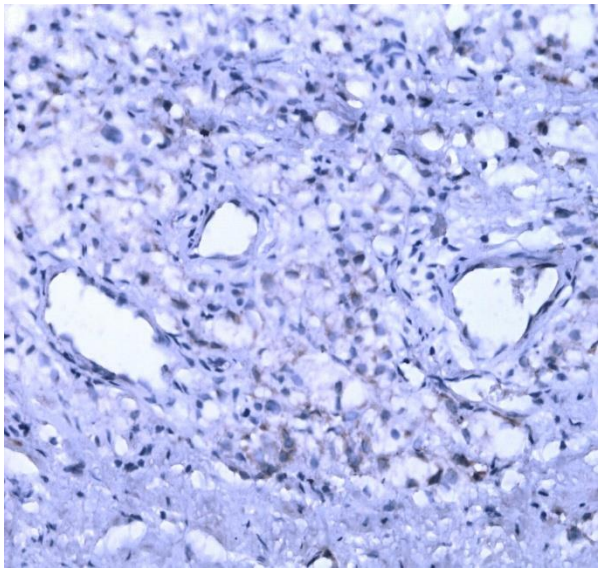
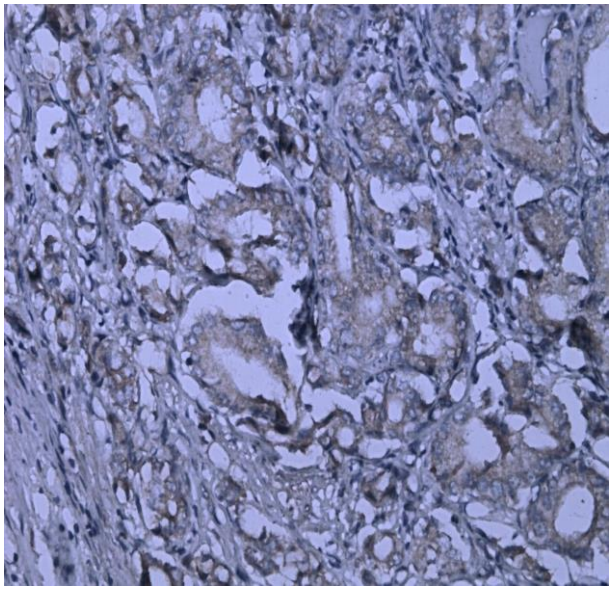


Figure 1. Preparation T. 3045/12, percentage >70%(3+) and intensity 1 MMP-2 intensity 1 score +



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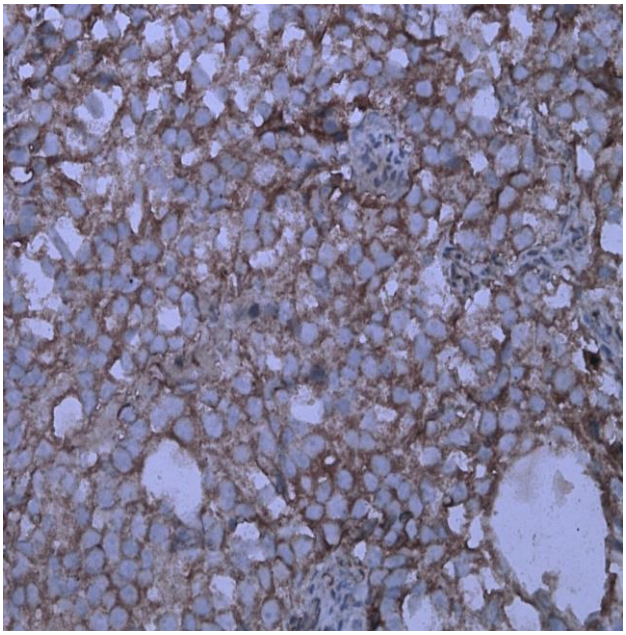

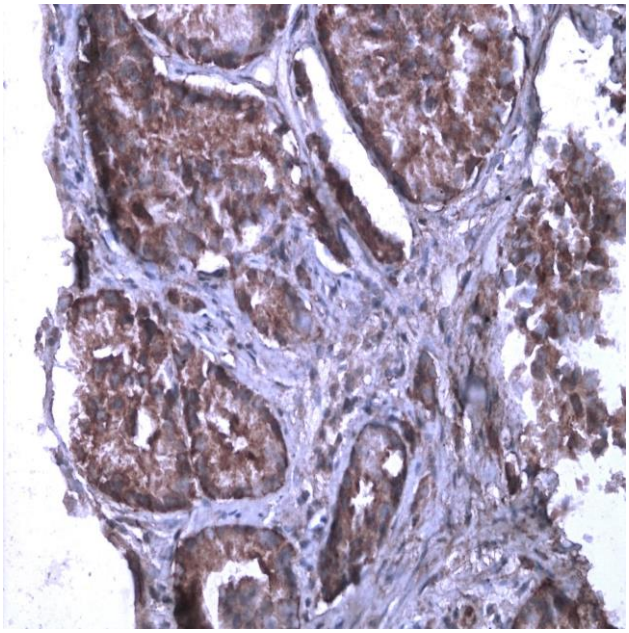

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2 Rosai, J. Male reproductive system. in Rosai and Ackerman's surgical pathology. vol.1, 9th ed, Elsevier, China, 2011; hh. 1361-87.
3 Epstein, JI. The lower urinary tract and male genital system, in Robbins pathologic basic of disease, 8th ed, Saunders, Philadelphia, 2010; hh. 993-1003.
4 Young, RH. Atlas of tumors pathology, tumors of the prostate gland, seminal vesicles, male uretra, and penis, 3rd series, Armed Forces Institute of Pathology, Washington DC, 2000; hh. 111-200.
5 Brehmer B, Biesterfeld S, Jakse G. Expression of matrix metalloproteinases (MMP-2 and -9) and their inhibitors (TIMP-1 and -2) in prostate cancer tissue, Prostate Cancer and Prostatic Diseases 6, 2003; 217–222. doi:10.1038/sj.pcan.4500657. http://emedicine.medscape.com/article/457394-overview
6 Nelson RA, Fingleton B, Rothenberg ML, Matrisian LM, Matrix metalloproteinases: Biologic activity and clinical implications, Journal of clinical Oncology, 2000, 218(5):1135-1149.
7 Duffy MJ, Maguire TM, Hill A, McDermott E, O'Higgins N. Metalloproteinases: role in breast carcinogenesis, invasion and metastasis. Breast cancer res. 2000;2(4):252 - 7.
8 Verma RP &Hansch C, Matrix metalloproteinase (MMPs) : chemical-biological function and (Q) SARs; 2007, Bioorg Med Chem 15(6) : 2223-68.
9 Tero Leinonen, Risto Pirinen, Jan Bohm, et al. Increased expression of matrix metalloproteinase-2(MMP-2) predicts tumour recurrence and unfavourable outcome in non-small cell lung cancer. In Histol Histopathol; 008; 23: 693-700 http://atlasgeneticsoncology.org/Genes/MMP2ID41396ch16q13.html
10 Daniel Kaemmerer, Luisa Peter, Emelie Lupp, et al. Original Article: Comparing of IRS as Immunohistochemical scoring schemes in gastroenteropancreatic neuroendocrine tumors. Int J Clin Exp Pathol ; 2012;5(3):187- 94
11 Stadiana Zivkovic. Original article : Correlation between proatate-specific antigen and histopathological difference of prostate carcinoma. In Arch Oncol; 2004; 12(3); 148-51
12 Nigel P. Murray, Gloria M. Calaf, Leonardo Badinez, et al. P504S expressing circulating prostate cells as a marker for prostate cancer. In Oncology Reports; 2010; 24; 687-92
13 Dominique trudel, Yves fradet, Franc, et al. Significance of mmp-2 expression in prostate cancer. An immunohistochemical study. In Cancer research ; 2003; 63; 8511–15
14 Yixuan Gong, Uma D. Chippada-Venkata, William K. Oh. Reviews: Roles of Matrix metalloproteinase and Their Natural Inhibitors in Prostate Cancer Progression. Cancers; 2014; 6 ; 1298-327
15 B Brehmer, S Biesterfeld, G Jakse. Prostate Cancer and Prostatic Disease: Expression of matrix metalloproteinase (MMP-2 and -9) and their inhibitors (TIMP-1 and -2) in prostate cancer tissue. 2003; 6; 217-22.
16 Romano Oguic, Vladimir Mozetic, Eleonora Cini Tesar, et al. Research article: Matrix metalloproteinase 2 and 9 Immunoexpression in Prostate Carcinoma at the positive Margin of Radical Prostatectomy Specimen. In Hindawi Publishing Corporation Pathology Research International ; 2014; Article ID 262195; 8. http://www.ncbi.nlm.nih.gov/gene/4313
17 Amalinei C, Caruntu ID, Balan RA. Biology of metalloproteinases, Romanian Journal of Morphology and Embryology, 2007; 48 (4) : 323-34.

18 Stankovic S, Konjevic G, Gopcevic K, Jovic V, Inic M, Jurisic V. Activity of MMP-2 and MMP-9 in sera of breast cancer patients. Pathology - Research and Practice. 2010;206(4):241-7.

Published Article

CORRELATION BETWEEN BLOOD SERUM PSA LEVEL AND MMP-2 IN PROSTATE ADENOCARCINOMA

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ABSTRACT

Objective: *This study aims to prove the correlation between Prostate Specific Antigen (PSA) blood level and Matrix Metalloproteinase-2 (MMP-2) expression in patients with prostate adenocarcinoma.* ***Material & method:*** *Prostate cancer patients' data from January 2009 to May 2012 were collected at the Department of Pathology, Soetomo General Hospital Surabaya. Data collected included patient medical documents, PSA blood examination, and histopathological examination. Histopathology slides and paraffin blocks of needle biopsies, Transurethral Resection of Prostate (TURP) and radical prostatectomy of prostate cancer patients were re-read, then the samples that met the inclusion criteria were stained by immunohistochemistry using antibodies MMP-2.* ***Results:*** *Data collection was done to obtain data samples of prostate cancer patients in 2009 to 2012 comprising as many as 22 patients between the ages of 52-91 years. Prostate adenocarcinoma in age of 70-79 was found in 8 patients, with a mean age of 68 years. PSA values obtained from medical documents were between 8.6-594.41 ng/ml. Spearman's test performed in this study showed a positive correlation (one-tailed) (correlation coefficient (r) 0431, $p < 0.05$) between blood PSA level and MMP-2 expression in patients with prostate adenocarcinoma.* ***Conclusion:*** *Blood PSA level correlates positively with MMP-2 expression in prostate adenocarcinoma.*

Keywords: *Prostate specific antigen, matrix metalloproteinase-2, prostate adenocarcinoma.*

ABSTRAK

Tujuan: *Penelitian ini bertujuan untuk membuktikan hubungan antara kadar Prostate Specific Antigen (PSA) darah dengan Ekspresi Matrix Metalloproteinase-2 (MMP-2) pada penderita Adenokarsinoma Prostat.* ***Bahan & cara:*** *Data arsip penderita kanker Prostat dikumpulkan di Departemen/SMF/Instalasi Patologi Anatomi RSUD Dr. Soetomo Surabaya, mulai Januari 2009 sampai Mei 2012. Pengumpulan data meliputi dokumen medik penderita, data pemeriksaan PSA darah, dan data pemeriksaan Histopatologi. Slide Histopatologi dan blok parafin hasil biopsi jarum, Transurethral Resection of Prostate (TURP) dan Radikal Prostatectomy penderita kanker prostat dibaca ulang, kemudian sampel memenuhi kriteria inklusi dipulas secara imunohistokimia dengan menggunakan antibodi MMP-2.* ***Hasil:*** *Pengumpulan data yang dilakukan memperoleh data sampel penderita kanker prostat pada tahun 2009 sampai 2012 sebanyak 22 orang, yang terjadi antara usia 52-91 tahun. Adenokarsinoma prostat terbanyak terjadi pada usia 70-79 yaitu 8 orang, dengan rerata pada usia 68 tahun. Nilai PSA yang didapatkan pada dokumen medik antara 8.6-594.41 ng/ml. Uji Spearman yang dilakukan pada penelitian ini diperoleh hasil korelasi yang positif (1-tailed) (koefisien korelasi (r) 0.431, $p < 0.05$) antara kadar PSA darah dan ekspresi MMP-2 pada penderita adenokarsinoma prostat.* ***Simpulan:*** *Terdapat korelasi positif antara kadar PSA darah dengan ekspresi MMP-2 pada adenokarsinoma prostat.*

Kata Kunci: *Prostate specific antigen, matrix metalloproteinase-2, adenokarsinoma prostat.*

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INTRODUCTION

Prostate cancer is a malignancy of the sixth most-common of all types of malignancies in the world, and becomes the second leading cause of death from cancer in men caused by the incidence of metastasis.[1,2] The incidence of prostate cancer in the United States amounted to about 29% of the incidence of all cancers and 10% of the causes of death.[2,3]

Factors contributing to the clinical application of prostate cancer, among others, are the level of Prostate Specific Antigen (PSA) in serum, Gleason grade, tumor stage, and operation edge.[4] These factors have been studied for the development of molecular prognostic markers in prostate cancer. Some literature suggests that malignant tumor cells produce some matrix that can degrade extracellular matrix (ECM), such as Matrix Metalloproteinase (MMP) family that plays a role in the invasion and metastasis of malignancy.[5]

PSA is produced by prostate gland luminal epithelial cells in the form of ductal and acinar, then secreted into the lumen of the gland and excreted along with semen within the seminal vesicles. In prostate cancer (adenocarcinoma) changes in luminal epithelial cells can penetrate and damage basal cells. Changes in luminal epithelial cells and damage in basal cells cause PSA out of the lumen and come into the blood circulation, resulting in increased concentration of PSA in the blood. The increase can be detected in the blood and used for post-therapy screening and evaluation of prostate cancer.[1,2,6]

Adenocarcinoma is a type of prostate cancer that is most commonly found, and in such malignancy there is an imbalance between MMP and Tissue Inhibitor Metalloproteinase (TIMP), which led the invasion into the surrounding tissue and the incidence of metastasis, both lymphogenic and hematogenous.[7-9] MMP-2 is a member of MMP family that has a special composition and function. MMP-2 (gelatinase A), in its function of invasion and metastasis, degrades collagen IV.[10] The invasion and metastasis that occurs in prostate adenocarcinoma can be assessed from the expression of MMP-2 in tumor cells.[11]

OBJECTIVE

The aim of this study was to prove the correlation between blood serum PSA level and MMP-2 in prostate adenocarcinoma, since studies on the correlation between blood serum PSA levels and MMP-2 expression in prostate adenocarcinoma is rare.

MATERIAL & METHODS

This study was an observational analytic study with cross-sectional approach conducted by collecting data from the archive on prostate cancer patients whose diagnosis was established histopathologically as adenocarcinoma of the prostate in the Department of Pathology, Soetomo General Hospital Surabaya, from January 2009 to May 2012. Data collected were in the form of medical documents of the patients, PSA blood examination and histopathological examination data. Histopathology slides and paraffin blocks of needle biopsies, TURP and Radical Prostatectomy from prostate cancer patients were collected, and then re-reading was done to those cases. Samples taken were patients who had data on blood serum PSA examination by ELISA and met the inclusion criteria. Immunohistochemical staining was done by using MMP-2 antibodies to eligible blocks. Results were obtained by conducting analytical testing with Spearman's correlation by comparing the patients' blood PSA with MMP-2 expression in tumor cells. The study was conducted at the Laboratory of Pathology, Faculty of Medicine, Universitas Airlangga, from May to August 2015.

Immunohistochemical staining on paraffin blocks of patients with a diagnosis of prostate adenocarcinoma was performed using antibodies MMP-2. Assessment of MMP-2 expression was done by assessing the expression in the cytoplasm or tumor cell membrane with staining intensity assessment and the percentage of stained tumor cells. Intensity scores are 0 = tumor cells not stained; 1 = light yellow; 2 = brownish yellow and 3 = brown, while the percentage of cell number is multiplied. The determination of the degree of expression was follows: 0 (negative) when the score is 0; 1+ = 1-3; 2+ = 4-6; and 3+ = 7-9.[12] Data on PSA and MMP-2 expression was tested using Spearman 'rho correlation test, with significant results if $p < 0.05$.

RESULTS

Data collection was done to obtain data on samples of prostate cancer patients from 2009 to 2012 as many as 22 people in ages of 52-91 years. Prostate adenocarcinoma occurred mostly in the age of 70-79, comprising 8 patients, with a mean age 68 years. PSA values obtained from medical documents were between 8.6 - 594.41 ng/ml.

All samples showed positive MMP-2 expression in the cytoplasm and tumor cells membrane, with the percentage as much as 30-70% and > 70%. The intensity varied from light yellow to brown. Then Spearman tests conducted in this study showed a positive correlation (one-tailed) (correla-

tion coefficient (r) 0.431, $p < 0.05$) between blood PSA level and MMP-2 expression in patients with prostate adenocarcinoma.

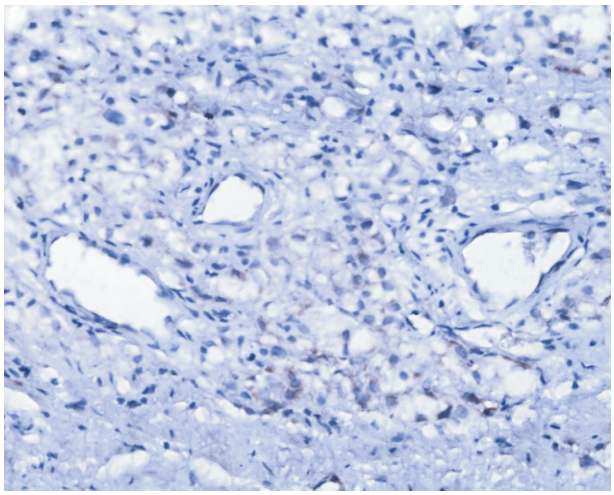


Figure 1. Preparation T. 3045/12, percentage > 70% (3+) and intensity 1 MMP-2 intensity 1 score +

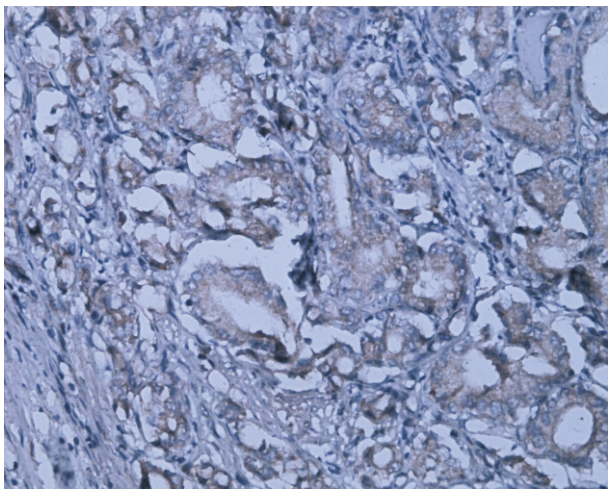
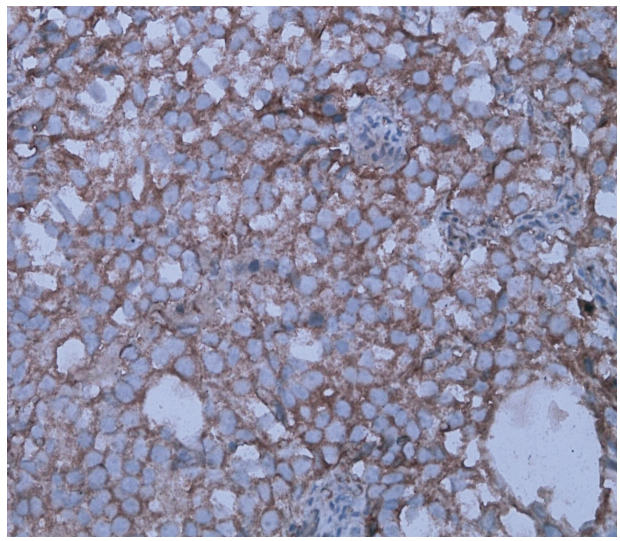


Figure 2. Preparation T. 1662/10 percentage > 70% (3+) and intensity 2.

Table 1. MMP-2 expression in prostate adenocarcinoma.

MMP-2 expression score	%	I	score
0	0	0	0
1	0	13	13
2	4	5	5
3	18	4	4
Total	22	22	22



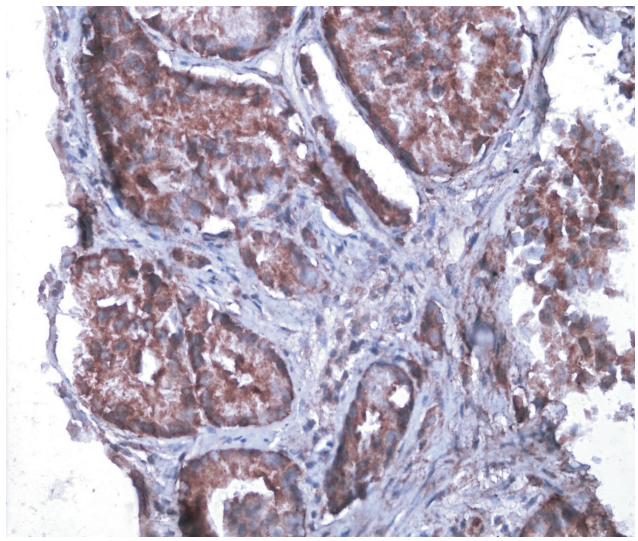


Figure 3. Preparation T. 3606/11 and 6324/10 percentage > 70% (3+) and intensity 3.

Blood PSA value in the sample was between 8.6–594.41 ng/ml, showing an increase in serum PSA level. Some literature mentions that the normal level is < 4 ng/ml, showing an increase in blood PSA levels compared to normal.[13,14]

DISCUSSION

The prostate is a retroperitoneal organ that surrounds the bladder neck and urethra, a gland shaped like a pear. Normal prostate gland is composed of two layers of cells: luminal epithelial cells and basal cells. Secretory/luminal cells have a

function to produce seminal fluid in the form of serine protease (prostate specific antigen/PSA).[1,2] Prostate cancer is most commonly in the form of adenocarcinoma, which is an invasive malignant tumor derived from luminal epithelial cells. In adenocarcinoma luminal epithelial cells change and able to penetrate basal cells, resulting in basal cell damage. Changes in luminal epithelial cells and damage in basal cells cause the produced PSA out of the lumen and enters blood circulation, resulting in increased PSA concentration in blood. The increase can be detected in blood and is used for screening and evaluation of prostate cancer post-treatment as well as indications for biopsy in patients. PSA is also a marker that is often used to diagnose prostate cancer.[1,2,6]

Murray in 2010 also stated that blood PSA value was positively related to the number of malignant epithelial cells stained with immuno-histochemical staining with PSA antibody. Increasing number of malignant epithelial cells results in increased blood PSA level, indicating that more malignant cells that damage the barrier will lead to higher levels of PSA detected in the circulation.[14]

The process of cell integrity disruption causes the release of PSA in circulation. This integration disorder also occurs in hyperplasia, inflammation and tumors. PSA value in benign prostate tissue: 0.5 ± 0.4 ng/ml, in BPH: 0:31 ± 0:25 ng/ml, so that up to now there is no definite value in cancer.[6]

Zivkovic in 2004 obtain levels of 4.0-10.0 ng/ml in benign hyperplasia, prostatitis and prostate cancer. Murray conducted a study in 2010 by measuring the weight of prostate tissue, giving results that each gram of prostate cancer tissue can increase PSA of approximately 2.3 ng/ml. Hyperplastic prostate tissue is 10 times lower than cancerous tissue. In addition, they also found that the highest PSA level was in the lumen of the prostate gland, and between gland lumen and capillary blood vessel, basal cells in the gland, prostate stromal and capillary endothelial cells they found barrier that prevents PSA to circulate in the circulation. Therefore, PSA can increase drastically in the state of prostatitis, but can return to normal after the infection resolved.[14]

All samples of this study showed positive expression of MMP-2, according to a study by Trudel (2003), who found that 70% of malignant epithelial cells had positive expression of MMP-2 due to the degradation of ECM by MMP-2.[15] There was a positive correlation between blood PSA levels with MMP-2 expression in prostate cancer, showing that increased blood PSA level is associated with increased MMP-2 expression in prostate cancer (correlation coefficient (r) 0.431, $p < 0.05$).

Malignant cells produce matrix that actively degrades with different specific substrates that act together in the degradation of Extracelluler Matrix (ECM), that is the Matrix Metalloproteinase (MMP) family, which is associated with the invasion and metastasis of tumor cells. This tumor metastases is the main cause of death in patients with cancer, particularly prostate cancer.[8,16]

Matrix Metalloproteinase (MMP), or matrix in, is a group of free endopeptidase structure that contain zinc, in cooperation with other proteolysis enzymes, such as cysteine proteinases, aspartic proteinase and serine proteinase, which plays a role in extracellular matrix degradation.[8,9] MMP is secreted in the form of proenzyme, then be activated by the proteolytic gap, and this process can be inhibited by Tissue Inhibitor Metalloproteinase (TIMP) in order to avoid degradation. Imbalance between MMP and TIMP is one of the causes of invasion and metastasis that occurs in malignant tumors.[7-10] Such imbalance is also an important factor that participates in tumor progression.[17] The expression of MMPs (MMP-2 and MMP-9) is often associated with tumor aggressiveness and overall survival, and it is also often used as a marker of malignancy.[18]

Degradation by MMP in malignancy process is taking place through several stages, including: 1) assisting the formation of a micro-environment through the release of extracellular matrix growth factor; 2) assisting the process of tumor angiogenesis, and enhancing the ability of the migration and invasion of tumor cells; 3) playing a role in angiogenesis at the site of metastasis; 4) playing a role in the damage to basal membrane of blood vessel walls, allowing intravasation and extravasation of tumor cells; and 5) playing a role in shaping new microenvirontment at metastasis site.[19]

Positive correlation between blood PSA levels with MMP-2 expression in prostate cancer showed that increased blood PSA level is associated with increased MMP-2 expression in prostate cancer (correlation coefficient (r) 0431, $p < 0.05$). Increased PSA levels in blood indicates barrier damage caused by invasion through the degradation of collagen type IV, as well as damage caused by MMP-2.[20]

According to Amalinei, Caruntu and Balan (2007), based on the substrate specificity, sequence similarity, and domain organization, MMP is divided into 6 groups: gelatinase (MMP-2, MMP-9); matrilysins (MMP-7, MMP-26); collagenases (MMP-1, MMP-8, MMP-13); stromelysin (MMP-3, MMP-10, MMP-11); membrane-type MMP (MT-MMP -> MMP-14, MMP-15, MMP-17, etc.); and other MMPs (MMP-12, MMP-19, etc.).[20]

Gelatinase-type MMP (MMP-2 and MMP-9) plays an important role because it can degrade collagen types IV, V, VII, X, XI, XIV, gelatin, elastin, proteoglycan core proteins, myelin basic protein, fibronectin, fibrillin-1, a precursor TNF-alpha and IL-1b. MMP-2 is able to break down collagen type I, which is the main component that forms the stroma and break down the molecular structure of collagen type IV which is a most protein constituent of basal membrane and the extra cellular matrix, which is instrumental in the invasion process.[7-10] Similarly, Murray in 2009 found that the expression of MMP-2 plays a role in the spread of malignant cells through invasion and metastasis.[14] MMP-2 expression (gelatinase A) in some malignant tumors has been widely studied. This relates to the prognostic value. Studies on the MMP-2 have also been started in prostate cancer (adenocarcinoma).

CONCLUSION

Blood PSA level correlates positively with MMP-2 expression in prostate adenocarcinoma and increased blood PSA can be used to predict ECM damage in MMP-2-induced prostate adenocarcinoma.

REFERENCES

1 Epstein, JI, Algaba, F, Allbrook, WC, Bastacky, S. Acinar adenocarcinoma, in WHO classification of tumours, pathology and genetics tumours of the urinary system and male genital organs, Ed. Ebk JN, IARC Press, Lyon; 2004. p. 161-92.

2 Rosai, J. Male reproductive system. In Rosai and Ackerman's surgical pathology. 9th Ed. Elsevier, China. 2011; 1: 1361-87.

3 Epstein, JI. The lower urinary tract and male genital system, in Robbins pathologic basic of disease, 8th Ed. Saunders: Philadelphia; 2010. p. 993-1003.

4 Young, RH. Atlas of tumors pathology, tumors of the prostate gland, seminal vesicles, male uretra, and penis, 3rd Series. Armed Forces Institute of Pathology: Washington DC; 2000. p. 111-200.

5 Brehmer B, Biesterfeld S, Jakse G. Expression of matrix metalloproteinases (MMP-2 and -9) and their inhibitors (TIMP-1 and -2) in prostate cancer tissue, Prostate Cancer and Prostatic Diseases 6; 2003. p. 217-22. doi:10.1038/sj.pcan.4500657.

6 http://emedicine.medscape.com/article/457394-overview

7 Nelson RA, Fingleton B, Rothenberg ML, Matrisian LM, Matrix metalloproteinases: Biologic activity and clinical implications, Journal of Clinical Oncology. 2000; 218(5): 1135-49.

8 Duffy MJ, Maguire TM, Hill A, McDermott E, O'Higgins N. Metalloproteinases: role in breast carcinogenesis, invasion and metastasis. Breast Cancer Res. 2000; 2(4): 252-7.

9 Verma RP, Hansch C. Matrix metalloproteinase (MMPs): chemical-biological function and (Q) SARs. Bioorg Med Chem. 2007; 15(6): 2223-68.

10 Tero Leinonen, Risto Pirinen, Jan Bohm. Increased expression of matrix metalloproteinase-2 (MMP-2) predicts tumour recurrence and unfavourable outcome in non-small cell lung cancer. In Histol Histopathol. 2008; 23: 693-700.

11 http://atlasgeneticsoncology.org/Genes/MMP2ID4136ch16q13.html

12 Daniel Kaemmerer, Luisa Peter, Emelie Lupp. Original Article: Comparing of IRS as immunohistochemical scoring schemes in gastroenteropancreatic neuroendocrine tumors. Int J Clin Exp Pathol. 2012; 5(3): 187-94

13 Stadiana Zivkovic. Original article: Correlation between prostate-specific antigen and histopathological difference of prostate carcinoma. In Arch Oncol. 2004; 12(3): 148-51.

14 Nigel P. Murray, Gloria M. Calaf, Leonardo Badinez. P504S expressing circulating prostate cells as a marker for prostate cancer. In Oncology Reports. 2010; 24; 687-92.

15 Dominique trudel, Yves fradet, Franc. Significance of MMP-2 expression in prostate cancer. An immunohistochemical study. In Cancer research. 2003; 63; 8511-15.

16 Yixuan Gong, Uma D. Chippada-Venkata, William K. Oh. Reviews: Roles of matrix metalloproteinase and their natural inhibitors in prostate cancer progression. Cancers. 2014; 6: 1298-327.

17 B Brehmer, S Biesterfeld, G Jakse. Prostate cancer and prostatic disease: Expression of matrix metalloproteinase (MMP-2 and -9) and their inhibitors (TIMP-1 and -2) in prostate cancer tissue. 2003; 6; 217-22.

18 Romano Oguic, Vladimir Mozetic, Eleonora Cini Tesar. Research article: Matrix metalloproteinase 2 and 9 immunoexpression in prostate carcinoma at the positive margin of radical prostatectomy specimen. In Hindawi Publishing Corporation Pathology Research International; 2014. Article ID 262195; 8.

19 http://www.ncbi.nlm.nih.gov/gene/4313.

20 Amalinei C, Caruntu ID, Balan RA. Biology of metalloproteinases. Romanian Journal of Morphology and Embryology. 2007; 48(4): 323-34.