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2015年度

笹川医学奖学金进修生同学会广东分会

互联网+时代的医生对策研讨会

主办单位：笹川医学奖学金同学会　日中医学协会

支持单位：国家卫生计生委　日本财团

会议时间：2015年10月11日（周日）

会议地点：广州珀丽酒店三楼牡丹厅

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笹川医学奖学金进修生同学会

地址：北京海淀区西直门北大街联慧路101号西晴公寓C座0248室

邮编：100029

电话：010-82211350　15901208067

微信：Tongxuehuibeijing

邮箱：sc1000@vip.163.com

网站：www.sskw.net

会议日程

•14：00-14：20

大会开幕式

1. 同学会秘书长李忠金先生致欢迎词
2. 中国工程院姚新生院士致辞
3. 日本国驻广州总领事斋藤法雄先生致辞
4. 日中医学协会山田阳城先生致辞

•14：20-16：00

学术交流

14：20-14：50

演讲一　演讲者：徐武华 教授

工作单位：广州市红十字会医院

题目：互联网+时代下的医生角色转变

14：50-15：30

演讲二　演讲者：丘勇超 教授

工作单位：广州中医药大学附属第一医院

题目：互联网时代的医生

15：30-16：00

演讲三　演讲者：王甲东 教授

工作单位：中山大学家庭医生杂志社

题目：互联网+时代的医生个人品牌打造

•16：00-16：20

集体拍照及茶歇

•16：20-17：30

自由发言交流时间

•18：00-20：00

晚宴

主讲人简介

徐武华

广州市红十字会医院主任医师

暨南大学博士生导师

广东省临床重点专科-广州市红十字会医院康复医学科（神经二科）高心亚科主任。2003年获笹川奖学金在日本冈山大学神经病态研究所进修。先后承担卫生部、中华医学会、广东省科技厅、广东省自然科学基金委员会、广东省卫生厅、广州市卫生局以及暨南大学和医院等10余项科研项目，共发表SCI论文3篇，国内核心期刊论文50余篇。中国医师协会老年医学分会全国委员、广东省医院管理协会康复管理分会副组长、广州市物理医学与康复学分会副主任委员，广州市神经病学会委员；中华医学会广东省分会神经病学委员会青委组组员。

丘勇超

广州中医药大学第一

附属医院泌尿外科主任

同时担任国际性医学学会/亚太性医学学会会员、国际老年男性研究会会员、国际中医男科学会第三届常务委员、亚洲男科学会会员、日本性机能学会会员、日本国横滨市立大学医学部第二外科客座研究员、中国性学会会员、中医中老年男子健康研究组（CHSAM）委员、中国翻译工作者协会会员、广东省优生优育协会专家委员会男性生殖健康专业委员会委员、广东省医学会医疗事故技术鉴定专家库成员、笹川医学奖学金进修生归国同学会理事会第20届理事会常务理事、《中国男科学杂志》编委、《中国性科学》杂志编委、《临床医学工程》杂志编辑委员会副主编等。

王甲东

中山大学教授

1987年获笹川奖学会赴日本学习。曾任中山大学家庭医生杂志社总编、中华医学会科普分会副主委、中国科普作家协会医药委员会副主委、中国科技期刊编辑学会医学委员会副主委、中国科技期刊期刊学会学术委员会副主委、中国卫生部新闻宣传中心专家咨询委员会专家、中国健康教育中心专家咨询委员会专家。现任广东省科普作家协会副理事长、广东省社会医学研究会心理咨询专业委员会副主委、《康非学报》编委、《中国科技期刊研究》编委、《中华生物医学工程杂志》编委。

项目活动报告

<table>
<tr><td colspan="3">活动名称：笹川同学会广东分会 2015 研讨会——在互联网+时代医生对策</td></tr>
<tr><td>时间：2015 年 10 月 11 日</td><td>地点： 广州珀丽酒店</td><td>人数： 36</td></tr>
<tr><td>报告人： 卢玄洁</td><td>期别：</td><td>手机：13828449822</td></tr>
<tr><td colspan="2">单位： 广州方橙健康科技有限公司</td><td>邮箱：13828449822@139.com</td></tr>
<tr><td>活动内容</td><td colspan="2">一、开幕及嘉宾致辞
1、同学会秘书长李忠金先生致辞
2、中国工程院姚新生院士致辞
3、日本国驻广州总领事斋藤法雄先生致辞
4、日中医学协会山田阳城先生致辞
二、主题演讲
1、徐武华教授《互联网+时代下的医生角色转变》
2、邱永超教授《互联网时代的医生》
3、王甲东教授《互联网+时代的医生个人品牌打造》
三、集体拍照及茶歇
四、自由发言及交流
五、晚宴</td></tr>
<tr><td>成果（亮点）</td><td colspan="2">一、本次同学会选题”互联网+时代的医生对策”。互联网+正在不断影响世界各行各业，中国医生职业生涯同样和互联网不断融合。本次选题新颖、符合时代发展潮流。
二、本次会议邀请了日本国驻广州总领事斋藤法雄先生及日中医学协会山田阳城先生参加。这有助于进一步推动中日人民关系友好发展。</td></tr>
<tr><td>改进建议</td><td colspan="2">明年同学会我们将会提早做时间安排，在广东同学会中征集各方意见，选取出更具特色和代表性的选题，进一步推动各位同学积极交流，维系同学情谊。</td></tr>
<tr><td>备注</td><td colspan="2"></td></tr>
</table>

事業報告

事業名称： 笹川同学会広東分会 2015 年検討会-相互ネットワークと新時代の医師の役割		
日時： 2015 年 10 月 11 日	場所：広州　珀麗酒店	参加者数：36 名
報告者： 盧玄潔	期：	携帯電話：13828449822
所属機関部署名： 広州方橙健康科技有限公司		E-mail:13828449822@139.com

活動内容	1 開会及び来賓挨拶 ① 同学会秘書長李忠金挨拶 ② 中国工程院姚新生院士挨拶 ③ 日本広州総領事館齋藤法雄総領事挨拶 ④ 日中医学協会山田陽城先生挨拶 2 講演 ① 徐武華教授(相互ネットワークと医師の役割の変化について) ② 丘永超教授(相互ネットワーク時代の医師) ③ 王甲東教授(相互ネットワークと現代の医師は如何に個人のブランドを打ち立てるか) 3 集合写真とコーヒーブレーク 4 質疑応答及び懇親 5 夕食会
成果	1 今回はテーマを「相互ネットワークと新時代の医師の役割」を設定した。相互ネットワークは世界のあらゆる領域に絶えず影響を及ぼしており、中国の医師の一生と相互ネットワークは絶えず融合している。今回のテーマは新しく、又、時代の発展の潮流に一致している。 2 今回は日本広州総領事の斎藤紀雄先生と日中医学協会の山田陽城先生が参加した。この事は、日中の人々の友好関係の推進の力となるものである。
提案	来年の交流会は早くから準備を行い、広州支部会の意見を集約し更に特色あるトピックなテーマを設定し、同学会会員の積極的交流を推進し、懇親を深めたい。

2015年笹川医学奖学金同学会

四川分会学术交流会日程

时间：2015年11月28日（周六）上午

地点：四川大学华西医院天使宾馆四楼会议室。

联系人：（8期生）刘爱民 13398174133

参加人数：笹川医学奖学金成都地区同学18-25人，学生若干

具体时间安排：

8:40-9:00　签到

9:00　　会议开始 介绍日方来宾及有关同学，同学会李忠金讲话

9:10-9:30　4期 冉玉平教授的交流报告 ：“婴幼儿血管瘤治疗新方法”

9:30-10:30　秘书长介绍2016年东京中日医学交流大会会议安排及组团动员。

10:30-10:50　休息（合影留念）

10:50-11:50　同学继续互动交流

10:50-11:10　1期 李庭谦教授的交流报告 ：“中药的毒性和不良反应”

11:10-11:30　25期 丁群芳教授的交流报告 ：“让我们平静而有尊严的老去-谈谈对老年人的姑息医疗和人文关怀”

11:30-11:50　18期 胡秀英教授的交流报告 ：“向世界最好的医院学管理”

Mayo Clinic

11:50---　　学术交流结束

12:00-13:30　酒店2楼包间午餐

13:30---　　餐后自由交流活动

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2015年笹川医学奖学金进修生
同学会四川分会学术交流会

主办单位：笹川医学奖学金进修生同学会、日中医学协会

支持单位：国家卫生计生委、日本财团

承办单位：笹川医学奖学金进修生同学会四川地区分会

2015 年 11 月 28 日

四川 • 成都

项目活动报告

<table>
<tr><td colspan="4">活动名称： 2015年笹川医学奖学金进修生同学会四川分会学术交流会</td></tr>
<tr><td colspan="2">时间：2015-11-28</td><td>地点： 成都</td><td>人数： 40</td></tr>
<tr><td colspan="2">报告人：刘爱民</td><td>期别：8 期</td><td>手机：13398174133</td></tr>
<tr><td colspan="3">单位： 中国医学科学院输血研究所</td><td>邮箱:ram99@163.com</td></tr>
<tr><td>活动内容</td><td colspan="3">日中医学协会来宾 冈野友宏 讲话
秘书长李忠金介绍 16 年东京中日医学交流大会会议安排及组团动员。

4 期 冉玉平教授的交流报告 ：“婴幼儿血管瘤治疗新方法”
1 期 李庭谦教授的交流报告 ：“中药的毒性和不良反应”
25 期 丁群芳教授的交流报告 ：“让我们平静而有尊严的老去-
谈谈老年人的姑息医疗和人文关怀”
18 期 胡秀英教授的交流报告 ：“向世界最好的医院学管理”
合影留念
午餐</td></tr>
<tr><td>成果（亮点）</td><td colspan="3">冉玉平教授的交流报告 ：“婴幼儿血管瘤治疗新方法”系世界首次发现的治疗方法，在与会同学和嘉宾中引起强烈反响。

同学们对 2016 年东京医学交流大会期待很高，都表示积极参加。</td></tr>
<tr><td>改进建议</td><td colspan="3">建议同学会建立全体同学范围的 QQ 群或者微信群，以方便信息传播。</td></tr>
<tr><td>备注</td><td colspan="3"></td></tr>
</table>

事業報告

事業名称： 2015 年笹川医学奨学金進修生同学会四川支部会学術交流会		
日時： 2015-11-28	場所：成都	参加者数：40
報告者： 劉愛民	期：8 期	携帯電話：13398174133
所属機関部署名： 中国医学科学院輸血研究所		E-mail:ram99@163.com
活動内容	日中医学協会　来賓岡野友宏先生の挨拶 李忠金秘書長が 2016 年東京で日中医学交流大会が開催されるので、支部会で組織的に動員をしてほしい旨話をした。 4 期　冉玉平教授講演：「乳幼児血管瘤の新治療法」 1 期　李庭謙教授講演：「中薬の毒性と不良効果」 25 期　丁群芳教授講演:「平静で尊厳ある老い方-老年の緩和医療と Humanistic care」 18 期　胡秀英教授講演：「世界最高の医院より管理を学ぶ」 記念撮影 昼食	
成果	冉玉平教授の「乳幼児血管瘤の新治療法」の講演は世界で初めて発見された治療方法であるので、同学会会員と来賓から強い反響があった。 会員は 2016 年東京で開催される医学交流大会に非常に期待しており、皆積極的に参加したいと表明した。	
提案	同学会は全会員を網羅する QQ を作成すれば、情報伝達は簡単になると考える。	

义诊活动报告

时间：2015 年 8 月 23-24 日	地点：吉林省珲春县人民医院
参加人员：裴海成、吴龙仁、金玉莲、李忠金	
报告人：李忠金	义诊人数：380 人

活动内容及经过	根据国家卫生计生委与日本财团签署的《中日笹川医学合作项目》协议规定，2015 年 8 月 23-24 日，笹川医学奖学金进修生同学会在吉林省珲春县人民医院开展了义诊活动。 参加义诊人员为笹川医学奖学金进修生同学会归国同学（4 人）。 本次义诊活动得到当地卫生行政部门和珲春县人民医院的高度重视。珲春县人民医院以及本县其他医疗单位的医务人员共计 380 人，参加了讲座和培训活动；义诊人员还分别进入各自科室（传染科、耳鼻喉科、内分泌科），与该科室的医务人员讨论疑难病例及具体的诊治方法；义诊人员还分别与各自科室的医生共同查房，就查房的流程、重点问诊事项、注意事项等进行了指导，并现场进行了演示。 本次义诊活动着重对当地医务人员进行培训教育，收到了良好的效果。与以往直接看病人相比，培训当地医务人员、提高当地医务人员的业务水平的义诊方式更符合当地的实际需求，更具有可持续性。
希望	希望派遣更多领域的专家来指导业务、并建立定期来院指导的机制。

ボランティア診療報告

事業名称： ボランティア診療	
日時：2015 年 8 月 23 日-24 日	参加者数：380 名
場所： 吉林省琿春県人民医院	同学会参加者:裴海成、呉龍仁、金玉蓮、李忠金
報告者： 李忠金	
所属機関部署名： 同学会	
活動内容と経過	国家衛生計生委と日本財団が調印した「日中笹川医学協力プロジェクト」協定に基づき、2015 年 8 月 23 日～24 日まで笹川医学進修生同学会は吉林省琿春県人民医院でボランティア診療を実施した。 ボランティア診療に参加した会員は 4 名であった。 今回のこのボランティア診療を当地の衛生行政部門は非常に重視し、琿春県人民医院およびその他の医療機関からも併せて380名の医療関係者が講義と研修に参加した。ボランティア人員は各々分かれて各専門の科(伝染科、耳鼻咽喉科、内分泌科)に入り、現地の医者と難しい症例の検討、具体的な診断治療法について討論した。又、各々の科の医師と共同で回診を行い、その課程で重点事項、注意事項などの指導を行い、実際にデモンストレーションを行った。 今回のボランティア診療は当地の医者への研修という意味で非常に高い成果を挙げた。 ボランティア人員が直接患者の治療を行うのではなく、当地の医療人員に研修を行うことで、医療人員のレベルを向上させることができるこの方式は当地の需要に応えるものであり、持続可能なものである。
案　提	もっと多くの領域の専門家を派遣し、定期的に来院指導できるようにしてほしい。

义诊活动报告

时间：2015 年 9 月 13-14 日	地点：甘肃省张掖市医院、临泽县医院
参加人员：景涛、孙大为、李忠金（同学会会员） 曹农、姚亚丽、刘健、董湘玉、杨克虎（兰州大学附属医院）	
报告人：李忠金	义诊人数：60 人，培训人数：约 100 人

活动内容及经过	根据国家卫生计生委与日本财团签署的《中日笹川医学合作项目》协议规定，2015 年 8 月 23-24 日，笹川医学奖学金进修生同学会在甘肃省张掖市医院和临泽县人民医院开展了义诊活动。参加义诊人员为同学会会员 3 人及兰州大学附属医院的 5 人。9 月 13 日在临泽县医院进行了以查房为主的活动。6 名医生分别与各自科室（妇产科、心内科、外科、儿科、重症监护）的医务人员进行了查房和病例讨论。孙大为同学专门为妇产科的医生进行了“宫颈癌标准化诊断和治疗”的讲座。 9 月 14 日，在张掖市医院进行了讲座和培训活动；义诊人员同样进入各个科室（妇产科、心内科、外科、儿科、重症监护），与该科室的医务人员讨论疑难病例及具体的诊治方法。孙大为同学专门为妇产科的医生进行了“宫颈癌标准化诊断和治疗”和“标准化查房的流程和注意事项”的专题讲座。 本次义诊活动着重对当地医务人员进行培训教育，收到了良好的效果。与以往直接看病人相比，培训当地医务人员、提高当地医务人员的业务水平的义诊方式更符合当地的实际需求，更具有可持续性。
希望	希望派遣更多领域的专家来指导业务、并建立定期来院指导的机制。

ボランティア診療報告

<table>
<tr><td colspan="3">事業名称：　ボランティア診療</td></tr>
<tr><td colspan="2">日時：2015 年 9 月 13 日-14 日</td><td>参加者数：60 名　研修人数：100 名</td></tr>
<tr><td colspan="2">場所：　甘粛省張掖市医院、臨澤県医院</td><td>同学会参加者:景涛、孫大為、李忠金
曹衣、姚亜麗、劉健、董湘玉、楊克虎(蘭州大学附属医院)</td></tr>
<tr><td colspan="3">報告者：　李忠金</td></tr>
<tr><td colspan="3">所属機関部署名：　同学会</td></tr>
<tr><td>活動内容と経過</td><td colspan="2">国家衛生計生委と日本財団が調印した「日中笹川医学協力プロジェクト」協定に基づき、2015 年 9 月 13 日～14 日まで笹川医学進修生同学会は甘粛省張掖市医院、臨澤県医院でボランティア診療を実施した。
９月 13 日は臨澤県医院で回診を主に活動を行った。６名の医師が分かれて各科(産婦人科、循環器内科、外科、小児科、重症看護)に入り、当地の医療関係者と回診と病例検討を行った。孫大為氏が「子宮頸がんの標準的診断と治療」の講演を行った。
9 月 14 日は張掖市医院で講演と研修活動を行った。6 名の医師が分かれて各科(産婦人科、循環器内科、外科、小児科、重症看護)に入り、当地の医療関係者と回診と病例検討を行った。孫大為氏が「子宮頸がんの標準的診断と治療」と「標準的回診の流れ及び注意事項」の講演を行った。
今回のボランティア診療は当地の医者への研修という意味で非常に高い成果を挙げた。
ボランティア人員が直接患者の治療を行うのではなく、当地の医療人員に研修を行うことで、医療人員のレベルを向上させることができるこの方式は当地の需要に応えるものであり、持続可能なものである。</td></tr>
<tr><td>案　提</td><td colspan="2">もっと多くの領域の専門家を派遣し、定期的に来院指導できるようにしてほしい。</td></tr>
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第３７期研究者研究報告会

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日本財団ビル会議室１、２

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Characteristic of Care Management Agencies Affect Expenditure on Home Help and Day Care Services: A Population-based Study in Japan

訪問介護と通所介護の費用への事業所特性の影響に関する研究

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Abstract

Aim: The financial interests of care management agencies may affect how care managers assist clients' use of long-term care insurance services. This study examined the relationship between clients' service expenditures and whether the home help and day care service agencies belonged to the same organization as the care management agency.

Methods: Population-based data were obtained from a suburban municipality in Japan. We investigated 4,331 persons with care needs certificates (levels 1–5), including those using home help (N=1,780) or day care (N=2,141) services. Data on the service expenditures and clients' and agencies' characteristics were analyzed using multiple linear regression analyses controlling for potential confounders.

Results: Home help service users spent an average of USD 558.1 ± 590.1 for home help service and day care service users spent USD 665.0 ±415.9 for day care service. Living alone, living in a condominium/apartment, higher care needs, more severe cognitive impairment, and lower use of other services were associated with higher home help service expenditure. Day care service expenditure increased with older age, female gender, higher care needs, more severe cognitive impairment, and higher physical function. Clients whose service agencies and care management agencies belonged to the same organization had higher expenditures even after adjusting for confounders (home help: β=0.126, $p = 0.007$; day care: β= 0.085, $p = 0.002$, respectively).

Conclusions: Financial interests of care management agencies significantly influence clients' service expenditure. We should develop an effective system to minimize this influence.

Introduction

Populations in developed countries are aging rapidly and Japan's aging is the fastest.[1] In response to this, the Japanese government launched a mandatory, public long-term care insurance (LTCI) system in April 2000 to ensure long-term care services as a universal entitlement for every adult of 65 years and older and aged 40–64 years with aging-related diseases.[2, 3] Since LTCI introduction, the numbers of recipients and service providers, as well as the total expenditures, have been steadily increasing.[3, 4] Consequently, information on LTCI service use is particularly important for controlling growing needs and providing quality services.

Many previous studies have examined factors associated with LTCI service use;[5–9] several have explored factors related to LTCI service expenditures, employing the Anderson-Newman model of healthcare utilization.[10] This model is intended to clarify the factors determining health service use; these factors are classified as predisposing, enabling, and need factors. Predisposing factors include age,[11, 12] gender,[11, 13] and marital status;[13] enabling factors include living alone[11, 12, 14] and serviceuse;[15] and need factors consist of serviceneeds,[13] functional disability,[11, 12, 15] cognitive decline,[11–13] and specific chronic diseases.[11, 13, 14]

In addition to the factors mentioned above, there has been concern that financial interests of care managers (CMs) and care management agencies might affect LTCI serviceuse.[1, 3, 16] Under Japan's LTCI, each client in need of care is assisted by a CM for care management and service use. CMs play pivotal roles in LTCI service, including assessing care needs, drawing up care plans, conducting referrals, monitoring care quality, and adjusting care plans when necessary.[17–19] CMs are employed by care management agencies, which are operated by several types of organizations, such as for-profit, medical care, and social welfare organizations. Many of these organizations provide not only care management but also specific, although separately managed, care services, such as home help, day care, and home-care nursing services. CMs can be employed by service provider agencies[1] and work as both CMs and care providers;[20] thus, it may be difficult for CMs to maintain neutrality, especially when providing referrals for service agencies. However, no study has examined whether financial interests of CMs and care management agencies influence LTCI service expenditure.

In an attempt to fill this gap, we focused on home help service (HHS) and day care service (DCS) and examined the association between HHS and DCS expenditure and the relationship between the care management and service-providing agencies, specifically whether the two types of agencies belonged to the same organization. DCS and HHS are widespread in-home services whose service use amount can be controlled. DCS is a commuting service delivered in community-based day service facilities for the elderly, where they are provided with personal care for bathing, toileting and eating, support for other daily life activities, physical exercises, and returned home the same day. For HHS, a home helper visits the individual in need of care to provide care and household assistance, such as meals, dressing, bathing, cleaning, and laundry. Thus, by focusing on these two services, the present study can provide valuable insights on the financial interests of care management in LTCI services.

Methods

Study design and participants

A secondary analysis of cross-sectional data collected by the Institute of Gerontology at the University of Tokyo was performed. Population-based data were obtained from a suburban municipality in Japan with a population of about 404,000 and an aging rate of 20% (aged $\geq$ 65 years) in 2010. In September 2010, there are 10,480 people who were certified by the LTCI; among them, 4,331 older people were certified as "care needs level" (levels 1–5) and used at least one type of LTCI in-home service. Of these, all persons who used HHS (N=1,780) or DCS (N=2,141) were included in the analyses.

Ethical considerations

Data on older adults' service use and their characteristics were retrieved from the municipal government. Personal identifying information was not disclosed. The Ethics Committee of the University of Tokyo approved this study.

Measures

This study analyzed data on clients' and agencies' characteristics and information about in-home LTCI service use (home help, home bathing, home-care nursing, home rehabilitation, day care, day rehabilitation, short-stay respite care, and assistive device rental).

The main outcome indicators were the monthly HHS and DCS expenditures submitted to the national insurer. Agency relationship was created as the main independent variable. HHS users were divided into two groups. If clients were served by a home help agency that belonged to the same organization with their care management agency, they were categorized into the "same group"; if clients were served by home help agencies that belonged to a different organization than their care management agency, they were categorized into the "different group." Similarly, DCS users were also stratified into "same group" or "different group."

In addition, the following control variables were used: predisposing variables (age and gender), enabling variables (family type, living arrangement, income, and number of other services used), need variables (care needs level and physical and cognitive function) and care management agency ownership (for-profit organizations, medical care organizations, social welfare organizations, and others). Family type was divided into living alone and living with others. The type of living arrangement was categorized into living in a house, living in a condominium/apartment, and living in a facility. Income was measured by LTCI premium levels (which are determined by income levels), ranging from stage 1 (a welfare recipient) to 16 (income of over USD 83,000 per year). Use of other in-home services types for HHS and DCS users was also included as a control variable.

Care needs levels ranged from the lowest (1) to the most severe (5). Physical function of clients was assessed in terms of activities of daily living (ADL), using the "degree of independent daily living for disabled elderly" criteria designated by the Japanese Ministry of Health, Labour and Welfare. Scores ranged from 1 (no impairment) to 9 (bedridden). Cognitive function was measured with "degree of independent daily living for demented elderly" criteria also designated by the Japanese Ministry of Health, Labour and Welfare. Scores ranged from 1 (slight impairment) to 8 (severe impairment).

Statistical analysis

Data on service expenditure and characteristics of older adult clients and agencies were summarized using descriptive statistics. Characteristics of HHS and DCS users between different agency relationship groups were compared using chi-square and t-tests. Bivariate analysis was then performed to examine associations between service expenditure and agency relationship, as well as other control variables, using Spearman's rank-order correlation analyses, t-test, and analysis of variance. Finally, multiple linear regression analyses were conducted to determine the associations between agency relationship and the HHS and DCS expenditure used by clients, adjusting for other factors. To examine and adjust interaction between severity of care needs and the agency groups, the interaction term of "care needs level × agency relationship" was also included as an independent variable. SPSS version 16.0 (SPSS Inc., Chicago, IL) was used for the analysis. The significance threshold was set at 0.05 (two-tailed).

Results

Description of the study population

Table 1 showed the characteristics of older adults and their service agencies and the monthly service expenditure. For both types of service recipients, the average age was≥ 80 years; most were female (nearly 70%) and lived with others (≥ 55%) in a house (≥70%). Service recipients used other in-home services besides the target HHS or DCS and for-profit organizations operated nearly half of care management agencies. The total amount of fees consumed by HHS and DCS users were USD 1,094.3±767.8 and USD 1,090.3±633.6, respectively. Participants spent an average

of USD 558.1 ± 590.1 for HHS and USD 665.0±415.9 for DCS. Of those, 34.9 % of DCS clients and 43.9%of HHS clients were classified into the same group.

Different characteristics of HHS and DCS users between two agency relationship groups were shown in Table 2. Focusing on the comparison of service expenditures between groups, total service expenditure did not significantly differ between the groups of DCS users, and in HHS users, clients from the same group had slightly higher total fees than those from the different group. Moreover, clients from the same group spent more on both DCS and HHS than those from different groups; the gap of the service expenditures between the two groups was greater in HHS users than in DCS users (USD 245.10 vs.USD 66.50, respectively).

Factors related to the HHS and DCS expenditure: bivariate analysis

Results of bivariate analysis for the relationships between HHS and DCS expenditure and every independent variable were presented in Table 3. In addition to the significant correlation between agency relationship and service expenditure, most of the control variables had significant associations with HHS expenditure, except gender and the number of other services used. Those of older age, female gender, higher care needs, and higher cognitive function had larger DCS expenditure.

Factors related to HHS and DCS expenditures: multiple linear regression analyses

Table 4 showed the factors associated with HHS and DCS expenditure from the results of multiple linear regression analyses. Living alone, living in a condominium/apartment, higher care needs, more severe cognitive impairment, and lower use of other services was associated with higher HHS expenditure. DCS expenditure increased with older age, female gender, higher care needs, more severe cognitive impairment, and higher physical function. After adjusting for these potential confounders, clients from the same groups had higher service expenditures for HHS and DCS than those from the different groups (HHS: β=0.126, p = 0.007; DCS: β= 0.085, p = 0.002, respectively). The model explained 25.4% of the variance in HHS expenditure and 18.5% in DCS expenditure.

Discussion

In the present study, we examined factors related to HHS and DCS expenditure, focusing on the relationship between care management and service-providing agencies. To our best knowledge, this is the first population-based study to examine the influence of potential financial interests in care management agencies on expenditure on LTCI services in Japan. Our findings could help develop a more effective care plan and care management system in the LTCI system.

We determined that HHS and DCS expenditure was significantly greater in cases where the service was provided by agencies in the same organization as the care management agency than in those where the services were provided by agencies indifferent organizations. We posit two possible reasons for this difference.

The main possible reason might be that CMs prioritize their own agency's profit in assisting clients in LTCI service use. One of the central philosophies of Japan's LTCI was the introduction of consumer choice and competition by allowing free choice of service agencies; this was intended to enhance service quality, efficiency, and equity.[21] However, CMs are very likely to recommend service agencies from their employing organization to clients and also to encourage clients to use more services from the service agency of their same organization, to improve their agency's profitability. In addition, we found that the proportion of care management agencies operated by for-profit organizations was 54.4% in HHS users, higher than 47.6% in DCS users; the gap of the service expenditure between the two types of agency relationship was also greater in HHS users than in DCS users. All these findings indicate that agencies' interests

exert an important influence on LTCI service expenditure. This is consistent with previous findings that LTCI service use was significantly greater among clients managed by private agencies than those managed by public agencies.[22] The following may enable users to choose service agencies freely and to receive the proper amount of services and thus improve overall effectiveness and efficiency: enhancement of CMs' care management skills, information disclosure about each agency's service patterns and quality, and supervision from third-party organizations.[17, 22]

Another possible reason for the aforementioned difference in service expenditure may stem from the pursuit of win-win outcomes. CMs may be well connected with their clients and service-providing agencies when the care management and service-providing agencies belonged to the same organization. Consequently, they are able to monitor clients' general needs adequately and drive clients and their families to use more services. In addition, clients who have serious conditions requiring emergency care could be better served because quickly and timely referrals could be conducted when the care management and service-providing agencies are under the same organizational umbrella; thus, more services might also be used. The large amount of service use might lead to preferable outcomes such as clients' improved physical and cognitive functions. Thus, in such a situation, clients' needs are better met and agencies also benefit more. However, these explanations need to be verified in future studies examining the influence of the relationship of care management and service-providing agencies on care management and care plan contents made by CMs.

Other than agency relationship, there were several factors associated with LTCI services expenditure; most factors were consistent with previous studies.[12, 13, 15] In our study, needs indicators (care needs and physical and cognitive function) were strong predictors of both HHS and DCS expenditure. However, the relationship between other predisposing or enabling factors and service expenditure was not as consistent as previous studies. For example, we found those living alone had higher HHS, consistent with a Netherlands study, [14] but no direct relationship was found in DCS users. Such variations might be due to different study populations and diverse structures of long-term care systems between countries. All of the factors related to HHS and DCS expenditure could enrich the knowledge of determinants of LTCI service use.

Despite the important implications of our findings, certain limitations should be noted. First, generalizability is limited because our data were obtained from a single city. Research in other cities, including urban and rural areas, is necessary to confirm our results. Second, the data did not include the characteristics of family caregivers, CMs, service providers, or the medical status of clients. The confounding effects of these variables on agency selection and service expenditures should be investigated in the future.

Despite these limitations, the present study provides important preliminary evidence that LTCI service expenditure is increased not only by individual predisposing, enabling, and need factors but also by the agencies' interests. Older people who used HHS or DCS from the same organization as their care management agency had significantly higher service expenditures than those who used services from different organizations. Although there is a lack of national survey data, we showed that a considerable proportion of clients (34.9% of DCS clients and 43.9% of HHS clients) were served by service agencies that were operated by same organization as their care management agencies. Our findings suggest that the financial interests of care management agencies may influence LTCI use. These results indicate the need for reforming the care management system to provide quality and fair LTCI services to older adults.

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Table 1 Characteristicsof older adults, service agencies, and service expenditure

	HHS users (N=1,780)			DCS users (N=2,141)		
	n		(%)	n		(%)
	mean	±	SD	mean	±	SD
Age	80.3	±	9.5	82.1	±	8.8
Gender						
Men	541		(30.4)	690		(32.2)
Women	1,239		(69.6)	1,451		(67.8)
Family type						
Living alone	788		(44.3)	678		(31.7)
Living with others	992		(55.7)	1,463		(68.3)
Living arrangement						
Living in a house	1,251		(70.3)	1,748		(81.6)
Living in a apartment	486		(27.3)	368		(17.2)
Living in a facility	43		(2.4)	25		(1.2)
Income (1–16)	3.9	±	2.6	4.2	±	2.4
Numbers of other services used (0–7)	1.4	±	1.1	1.2	±	1.0
Physical function (1–9)	5.2	±	1.7	4.8	±	1.5
Cognitive function (1–8)	2.9	±	1.7	3.4	±	1.6
Care needs level (1–5)	2.3	±	1.3	2.2	±	1.2
Care management agency ownership						
For-profit organization	968		(54.4)	1,019		(47.6)
Medical organization	237		(13.3)	226		(10.6)
Social welfare organization	455		(25.6)	778		(36.3)
Others	120		(6.7)	118		(5.5)
Agency relationship						
Same group	781		(43.9)			(34.9)
Different group	999		(56.1)			(65.1)
Total service expenditure	1,094.3	±	767.8	1,090.3	±	633.6
HHS or DCS expenditure	558.1	±	590.1	665.0	±	415.9

HHS, home help service; DCS, day care service; SD, standard deviation.

Table 2 Comparison of characteristics of HHS users and DCS users between different agency relationship groups

	HHS users (N=1,780)			DCS users (N=2,141)		
	Same group	Different group	*P-value*	Same group	Different group	*P-value*
Age	81.0 ± 9.4	80.0 ± 9.6	0.015*	83.7 ±7.9	81.1 ±9.1	<0.001***
Gender						
Men	559 (71.6)	680 (68.1)	0.110	538 (72.0)	913 (65.5)	0.002**
Women	222 (28.4)	319 (31.9)		209 (28.0)	481 (34.5)	
Family type						
Living alone	389 (49.8)	399 (39.9)	<0.001***	238 (31.9)	440 (31.6)	0.888
Living with others	392 (50.2)	600 (60.1)		509 (68.1)	954 (68.4)	
Living arrangement						
Living in a house	494 (63.3)	757 (75.8)	<0.001***	623 (83.4)	1125 (80.7)	0.026*
Living in an apartment	256 (32.8)	230 (23.0)		111 (14.9)	257 (18.4)	
Living in a facility	31 (4.0)	12 (1.2)		13 (1.7)	12 (0.9)	
Income	3.8 ± 2.5	4.0 ±2.6	0.109	3.7 ±2.3	3.9 ±2.6	0.023*
Numbers of other services used	1.3 ±1.0	1.5 ±1.1	<0.001***	1.1 ±1.0	1.2 ±1.0	0.001**
Physical function	5.1 ±1.7	5.2 ±1.7	0.056	4.8 ±1.5	4.8 ±1.5	0.692
Cognitive function	3.0 ±1.7	2.8 ±1.8	0.007**	3.5 ±1.6	3.3 ±1.6	0.002**
Care needs level	2.3 ±1.3	2.3 ±1.3	0.839	2.2 ±1.2	2.2 ±1.2	0.577
Care management agency ownership						
For-profit organization	567 (72.6)	401 (40.1)	<0.001***	290 (38.8)	729 (52.3)	<0.001***
Medical organization	32 (4.1)	205 (20.5)		24 (3.2)	202 (14.5)	
Social welfare organization	152 (19.5)	303 (30.3)		396 (53.0)	382 (27.4)	
Others	30 (3.8)	90 (9.0)		37 (5.0)	81 (5.8)	
Total service expenditure	1,156.7 ± 776.9	1,045.5 ± 757.5	0.002**	1,089.1 ± 604.8	1,091.0 ± 648.7	0.946
HHS or DCS expenditure	695.7 ± 645.8	450.6 ± 518.1	<0.001***	708.3 ± 409.7	641.8 ± 417.5	<0.001***

Characteristics of HHS and DCS users between two groups are compared using chi-square and t tests.

*P<0.5; **p<0.01; ***p<0.001

HHS, home help service; DCS, day care service; SD, standard deviation.

Table 3 Factors related to expenditure on HHS and DCS

	HHS expenditure	*P*-value	DCS expenditure	*P*-value
	γ or Mean±SD		γ or Mean±SD	
Age[†]	0.065	0.006**	0.089	<0.001*
Gender[‡]				
Men	550.4±599.9	0.715	632.4±401.4	0.012*
Women	561.5±586.0		680.5±421.8	
Family type[‡]				
Living alone	653.3±640.6	<0.001***	646.6±391.0	0.163
Living with others	482.6±535.2		673.5±426.8	
Living arrangement[‡]				
Living in a house	516.3±556.4	<0.001***	673.4±421.0	0.056
Living in a condominium/apartment	669.9±658.6		634.8±392.7	
Living in a facility	513.1±574.9		518.4±346.6	
Income[†]	-0.112	<0.001***	0.032	0.145
Numbers of other services used[†]	0.01	0.681	-0.04	0.062
Physical function[†]	0.222	<0.001***	0.037	0.087
Cognitive function[†]	0.267	<0.001***	0.303	<0.001***
Care needs level[†]	0.315	<0.001***	0.316	<0.001***
Care management agency ownership[‡]				
For-profit organization	646.5±639.7	<0.001***	660.4±429.6	0.758
Medical organization	466.5±542.5		680.7±419.7	
Social welfare organization	437.4±477.9		670.9±396.6	
Others	487.1±532.9		636.0±414.6	
Agency relationship[‡]				
Same group	695.7±645.8	<0.001***	708.3±409.7	<0.001***
Different group	450.6±518.1		641.8±417.5	

[†]The relationships between the continuous variables and service expenditure were examined using Spearman's rank-order correlation analyses.

[‡]The relationships between the dichotomous or categorical variables and service expenditure were examined using t-tests or analyses of variance.

*p<0.05; **p<0.01; ***p<0.001.

HHS, home help service; DCS, day care service.

Table 4 Predictors of expenditure on HHS and DCS

	HHS users (N=1,780)			p-value	DCS users (N=2,141)			p-value
	β	95%CI			β	95%CI		
Age	0.003	0.000	0.006	0.068	0.002	0.001	0.004	0.010
Gender (0=male, 1=female)	-0.015	-0.070	0.040	0.597	0.037	0.008	0.067	0.014
Family type (0= alone, 1= with others)	-0.169	-0.218	-0.119	<0.001	-0.022	-0.050	0.005	0.114
Living arrangement								
Living in a house	ref.							
Living in an apartment	0.066	0.013	0.120	0.016	0.005	-0.028	0.037	0.784
Living in a facility	-0.199	-0.044	-0.353	0.012	-0.083	-0.194	0.028	0.142
Income	-0.010	-0.020	0.000	0.051	0.005	-0.001	0.011	0.084
Care needs level	0.181	0.121	0.241	<0.001	0.092	0.053	0.132	<0.001
Physical function	-0.002	-0.023	0.018	0.813	-0.033	-0.044	-0.022	<0.001
Cognitive function	0.036	0.021	0.051	<0.001	0.023	0.014	0.031	<0.001
Numbers of other services used	-0.090	-0.115	-0.065	<0.001	-0.060	-0.074	-0.046	<0.001
Care management agency ownership								
For-profit organization	ref.							
Medical organization	-0.035	-0.018	0.039	0.353	0.009	-0.033	0.050	0.683
Social welfare organization	-0.043	-0.098	0.012	0.129	0.004	-0.023	0.031	0.761
Others	-0.047	-0.142	0.048	0.330	-0.025	-0.079	0.029	0.358
Agency relationship (0=different,1= same)	0.126	0.034	0.218	0.007	0.085	0.032	0.138	0.002
Care needs level ×agency relationship	-0.025	-0.059	0.009	0.154	0.016	-0.006	0.037	0.155
Adj. R^2				0.254				0.185

HHS, home help service; DCS, day care service; CI: confidence interval

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《一年間の研究業績》

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演　　　題(研究题目)	Care Management Agency Affects the Service Cost of Home Help and Day Care: A Population-based Study in Japan		
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共同演者名(共同演讲者)			

■学会誌等に発表した論文（投稿中、掲載予定も含む）

学会杂志上发表的论文（含正在投稿中以及预定登载的论文），请使用论文**原文的语言**填写

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Molecular epidemiological study of extended-spectrum beta-lactamase producing *Proteus mirabilis* in Japan

臨床材料から分離される病原体の分子生物学的手法に基づく菌種同定および耐性因子の特定法の構築

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Abstract:

A total of 144 cefpodoxime-resistant *Proteus mirabilis* isolates were collected by a nationwide surveillance program during 2010 to 2013. Forty-four hospitals were precipitated in this surveillance. We demonstrated a molecular epidemiological study using whole-genome sequencing. 75 % (108/144 isolates) of ESBL encoding gene was identified $bla_{\text{CTX-M-2}}$. Tested 108 *P. mirabilis* isolates was classified in 9 different clades by the SNPs based core genome analysis. Furthermore clade 1 (77.1%, 84 isolates) was belonging to 9 sub-clades in clade 1. Clade 1-8 (11 isolates) was isolated from Hokkaido area. We analyzed deeply whole-genome sequence of $bla_{\text{CTX-M-2}}$ gene carrying plasmid from 11 isolates of sub-clade 1-8. In this study, we were success to take complete sequences of $bla_{\text{CTX-M-2}}$ gene carrying plasmids from 11 isolates. These 11 plasmid sizes were approximately 38.9 Kbp and similar structure shard each other. Furthermore, similar structure plasmid has been reported as 36 Kbp plasmid pHI4320 from *P. mirabilis*. This pHI4320 had no $bla_{\text{CTX-M-2}}$ and ISEcp*1*. From present study strongly indicates that pHI4320 is an ancestor of 11 plasmids of sub-clade 1-8.

Key Words:

Proteus mirabilis, Extended-spectrumβ-lactamase (ESBL), molecular epidemiology, whole-genome sequencing

Introduction:

Extended-spectrum β -lactamase(ESBL)-producing Enterobacteriaceae have been reported more and more in the world since their first description in 1983(1,2). SHV-2 is the first ESBL that identified in a Germany clinical isolate of *Klebsiella ozaenae* (3). The ESBL-producing *E.coli* of Toho-1-type (renamed CTX-M-44) isolate recovered in 1993 from a 1-year-old female child was reported from Japan in 1993 (4). The high prevalence of CTX-M ESBL genes have been documented the entire world in *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus mirabilis* (5). Treatment of infections caused by *E. coli* is becoming a serious problem including β -lactams (6). In China, ESBL-producing bacteria have become widely disseminated since at least 1994 (7). In 2014, Chinese investigators reported that the prevalence of ESBLs producing strains was 55.8% in *E. coli*, 29.9% in *Klebsiella spp*, and 24.0% in *P. mirabilis* isolates, respectively (8). In Japan, CTX-M-type ESBL producing Enterobacteriaceae are mainly isolated from nosocomial infections (9). During 2001-2003, a Japanese group surveyed the spread status of $bla_{\text{CTX-M}}$ genes from 1456 isolates, 21.8% were found to harbor this gene (10). From 2003-2009 of 2304 isolates 202(8.8%) were found to be ESBL producers, which include *E. coli*, *K. pneumonia* and *P. mirabilis* (11).

Previously, concerning ESBL producing *P. mirabilis* from clinical specimens, water, soil and domestic animals reported from Taiwan, China and Japan. From these reports, CTX-M-2 is predominant ESBL in *P. mirabilis* (12-19). However, these reports did not provide reason of spreading mechanism and genetic environment of around $bla_{\text{CTX-M-2}}$ in *P. mirabilis*. We collected 108 $bla_{\text{CTX-M-2}}$ gene carrying *P. mirabilis* clinical isolates collected by nationwide

surveillance programs in Japan. In this study, we demonstrated a whole-genome sequence analysis for 108 *P. mirabilis* isolates. One hundred-eight *P. mirabilis* isolates classified in 9 major clades and 9 sub-clades in clade 1. Seventeen *P. mirabilis* isolated from Hokkaido region were belonging to clade 1-1 (3 isolates), clade 1-8 (11 isolates), clade 2 (1 isolate) and clade 4 (2 isolates). The aim of this study is to understand the detailed $bla_{CTX\text{-}M\text{-}2}$ carrying plasmids from clade 1-8 *P. mirabilis* isolated from Hokkaido region.

Materials and Methods:

1. Bacterial isolates

One hundred thirteen ESBL-producing *P. mirabilis* isolates collected from nationwide in Japan during 2010 to 2013. All isolates were isolated from clinical samples and identified as *P. mirabilis* using a preferring identification system at 44 hospitals. Fifty-nine isolates were from urine, 23 from sputum, 8 from blood, 7 from pus, 7 from other samples, 4 from tracheal tube, 2 from decubitus ulcer, 2 from stool, 1 from bile and 1 from intra catheter. Seventy-nine (69.3%) of the isolates were isolated from inpatients. The inpatients or outpatients source of the remaining 27 isolates could be determined. The mean age of patients from whom *P. mirabilis* isolates was covered 71.2 years. 55 (48.3%) female patients of the isolates were isolated.

2. Whole-genome sequencing

To determine the whole genome sequence, genomic and plasmid DNA were extracted from all isolated colony of the microorganism by phenol-chloroform and QIAquick PCR Purification Kit (Qiagen, Chatsworth, CA, USA). The DNA libraries, prepared by the Illumina Nextera XT DNA Library Preparation Kit and MiSeq reagent kit v3 (Illumina Inc., San Diego, CA, USA), was analyzed by MiSeq sequencer (Illumina). CLC genomics workbench software was applied for assembling the short reads (300 bp). Based on the WGS data, identified antimicrobial resistance genes and plasmid typing were performed using ResFinder and PlasmidFinder web services (Center for Genomic Epidemiology Server), respectively. The core genome based phylogenetic analysis was performed with RAxML(bootstrapping with 1000 repetitions) using short reads of 145 *P. mirabilis* clinical isolates and 37 available genomic sequences of *P. mirabilis*. To extract single nucleotide variations, the short reads were aligned to *P. mirabilis* strain BB2000 (GenBank accession No. NC_022000.1) as a reference sequence using bwasw software (v.0.7.10). All mutation sites were extracted by SAMtools (v.1.3) and VarScan (v.2.3.7) software with the default parameters.

Results:

1. Distribution of extended-spectrum β -lactamase-producing *P. mirabilis* in Japan

Fig.1 shows the distribution of ESBL-producing *P. mirabilis* isolates among the eight regions of the main island of Japan. Geographically, these regions span from Hokkaido prefecture in the northeast to Kyusyu prefecture in the southwest. The highest rate of ESBL-producing *P. mirabilis* was in isolates recovered in Hokkaido and Tohoku (40.4%), followed by Kanto region (25.4%) and Kinki region (14.0%). The isolation rates of ESBL-producing *P. mirabilis* in Chubu region, Chugoku region, Kyusyu region and Shikoku region were 5.3%, 5.3%, 3.5% and 0.9%, respectively.

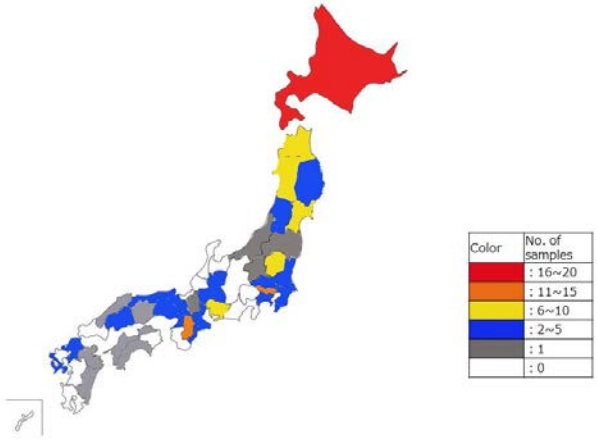

Fig.1.Distribution of ESBL-producing *Proteus mirabilis* isolates among regions of Japan.

4. Phylogenetic Analyses

A total of 180 isolates (including ESBL-producing, non-ESBL producer and 35 data base from National Center for Biotechnology Information) were chosen for global phylogenetic analysis. Currently, nine distinct phylogenetic clades designated from 1 to 9 are described (Fig. 2). Clade 1 delivered to 9 sub-clades. Eight of nine clades include $bla_{\text{CTX-M-2}}$ isolates. *P. mirabilis* isolates from Hokkaido region was belonging to sub-clade number 1-8 (11 isolates) and 1-4 (4 isolates). These results indicate that clade number 1-8 was spreading only Hokkaido region. However isolates in clade 1-4 were spreading in Hokkaido region (3 isolates) and in Kinki region (1 isolate). However some clades *P. mirabilis* isolates were spreading plural regions. For example, sub-clade 1-1 (19 isolates) was distributed Tohoku region, Kanto region, Kinki region and Chugoku region.

We have been success to analyzed *P. mirabilis* TUM11520 in 1-8 *P. mirabilis* (Fig. 3). This plasmid shows high similar with pHI4320 (Fig. 4).

One hundred-eighty *P. mirabilis* were analyzed by the next-generation sequencer to take whole-genome sequence. Genetic environment around $bla_{\text{CTX-M-2}}$ gene in clade 1-8 (11 isolates) was analyzed by *in silico* experiment. Sub-clade 1-8 *P. mirabilis* sheared almost the same genetic environment in plasmids (Fig. 5).

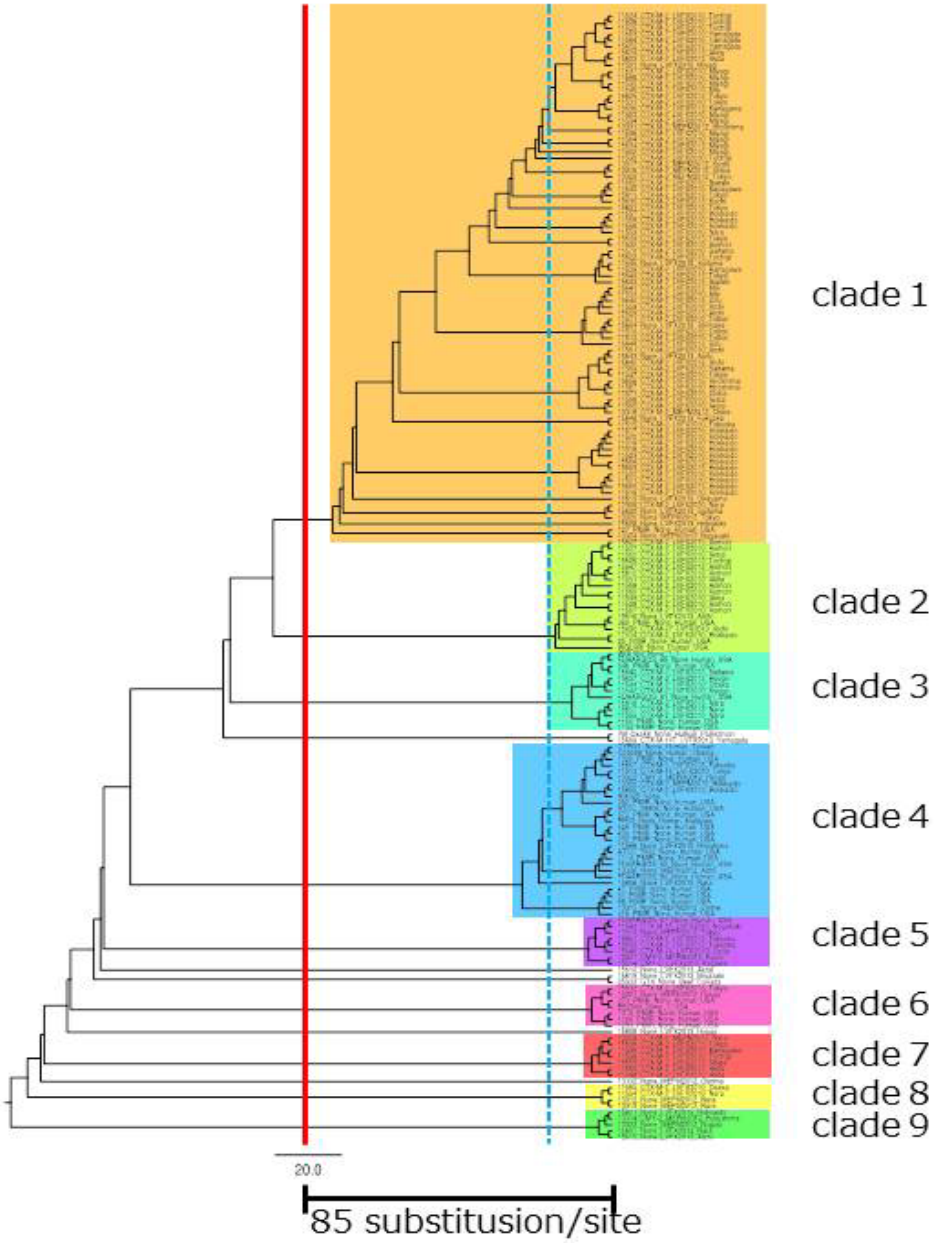

Fig. 2. Single Nucleotide Polymorphism tree based core genome in *Proteus mirabilis*

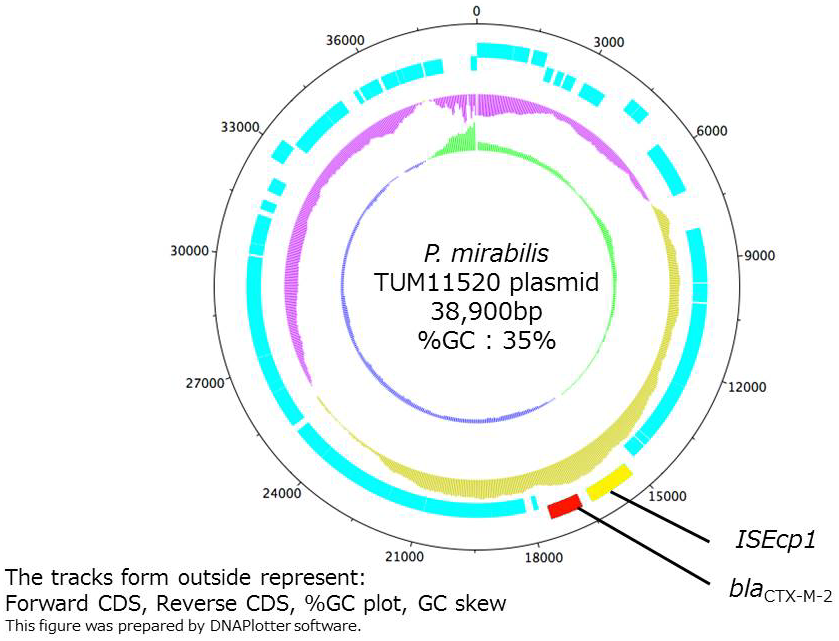

Fig.3 Complete sequence of *bla*$_{CTX-M-2}$ harbor plasmid from *P. mirabilis* TUM11520

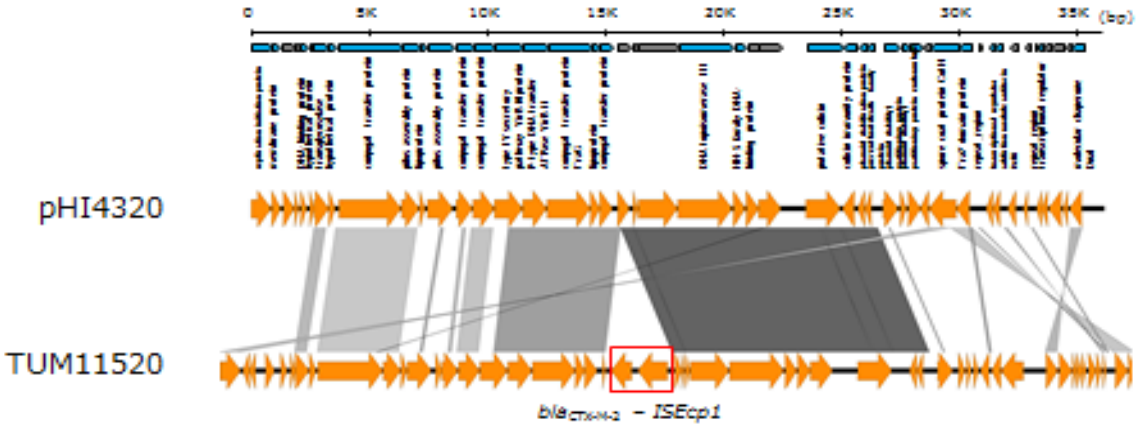

Fig. 4 Comparison of structure genes between plasmid pHI4320 and plasmid from TUM11520

Fig. 5 Comparison of whole-genome sequence data of sub-clade 1-8 harbor plasmid.

Discussion

A 2004 survey reported 11(16.7%) of 66 *P. mirabilis* isolates as ESBL-producers (21). A 2010 survey reported 28 (37.8%) of the 74 *P. mirabilis* of isolates as ESBL-producers (22). There is a trend of increased isolation of ESBL-producing *P. mirabilis* in Japan.

In Japan, predominant $bla_{\text{CTX-M}}$ group in *P. mirabilis* was thought to be the $bla_{\text{CTX-M-2}}$; $bla_{\text{Toho-1}}$ also belonging to the $bla_{\text{CTX-M-2}}$ group (20). One hundred-eight (95. 6%) isolates in ESBL producers harbored $bla_{\text{CTX-M-2}}$ encoding gene.

Recently, the dissemination of community-acquired infection causing of ESBL-producers of the CTX-M type ESBL is serious problem in the world. Some investigators reported that patients who are more likely to have risk factors such as elderly and receiving antimicrobial therapy (23, 24). In this study, the mean age of the patients was 71.2-year old with 69.3% of the isolates from hospitalized patients (data not shown).

The ESBL-encoding genes, especially $bla_{\text{CTX-M-2}}$ positive *P. mirabilis* isolates were disseminated in Japan. Some genetically related *P. mirabilis* isolates such as sub-clade 1-8 and 1-4 were from Hokkaido region. However $bla_{\text{CTX-M-2}}$ positive *P. mirabilis* in other clades were isolated from different regions. For example, sub-clade 1-7 *P. mirabilis* were spreading to Tokai region, Kanto region, Chugoku region and Tohoku region. Recently, UK investigator reported that ESBL producers were frequently detected in food products such as meats (25). Unfortunately, we could not clarify the infection source of $bla_{\text{CTX-M-2}}$ positive *P. mirabilis.* It is necessary to continue the surveillance of antibiotic resistant organisms for not only from human but also from environment, agriculture products, domestic animals and foods.

Present study, we determined 38.9 Kbp complete plasmid sequences of *P. mirabilis* TUM11520 belonging to clade 1-8 (Fig. 3). This plasmid show highly similarity to pHI4320 by *in silico* analysis (Fig. 4). Moreover, plasmids from clade 1-8 *P. mirabilis* show almost same structure exception of some gaps (Fig. 5). This data strongly suggests that pHI4320 is an ancestor of 11 plasmids of sub-clade 1-8 *P. mirabilis* from Hokkaido region.

In conclusion, the complete whole plasmid genome sequences of sub-clade 1-8 *P. mirabilis* were taken in this study. Our data suggest that sub-clade 1-8 $bla_{\text{CTX-M-2}}$ positive *P. mirabilis* spreading only Hokkaido region in 2010 to 2013. However, we confirmed widely disseminated *P. mirabilis* clades in this study. It will be necessary to clarify the infection source of $bla_{\text{CTX-M-2}}$ positive *P. mirabilis* in Japan.

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《一年間の研究業績》

■学会、研究会、報告会等での発表(在学会、研究会、报告会等的发表，请使用发表**原文的语言**填写)

演　　題(研究题目)	Isolation and characterization of expanded-spectrum cephalosporin-resistant Enterobacteriaceae from companion animals		
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共同演者名(共同演讲者)	Kotara Aoki, Makiko Yamamoto, Yoshikazu Ishii, Kazuhiro Tateda		

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共同演者名(共同演讲者)			

Endovascular therapy of wide-neck aneurysms using the LVIS Jr. stent: Two case reports
広頚脳動脈瘤に対するLVIS Jr.ステント支援下血管内治療の2例

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Abstract

Many vascular reconstructive devices are being developed to improve the endovascular therapeutic efficiency of intracranial aneurysms. A new intracranial stent: the Low-profile Visualized Intraluminal Support Junior (LVIS Jr.) stent, was authorized and has become available in Japan. We report two cases of wide-neck aneurysm treated with the LVIS Jr. stent. The Y-stent-assisted coil embolization was adapted for both cases. We achieved a good outcome in Case 1; however, in Case 2, there were hemorrhagic complications. Further experience is needed to confirm the applicability, durability, efficacy, and safety of this stent.

Key Words: endovascular therapy, wide-neck aneurysm, intracranial stent, stent-assisted technique

Introduction

For treating wide-neck aneurysms, many instruments are being developed to improve the endovascular therapeutic efficiency, including assisting devices such as balloons and intracranial stents. Wide-neck aneurysms sometimes arise at the origin of a vessel's terminal bifurcation, such as the basilar artery tip, the middle cerebral artery bifurcation, or the A1-A2 junction. In these aneurysms, the diameter of the surrounding vessel lumen is small and the angle of vessels diverging from the aneurysmal neck is often sharp. These confounding situations continue to make endovascular therapy challenging even when assisted techniques are used. The Low-profile Visualized Intraluminal Support Junior (LVIS Jr.) stent (MicroVention, Tustin, CA, USA) was developed to break the therapeutic toughness of wide-neck aneurysms. This stent, which has a diameter of 2.5 mm and can be deployed in 2-mm diameter vessels, can be delivered through a 0.017-inch microcatheter. Moreover, this stent is soft and, for a braided structure, resists comparative study of its strength and flexure. We report two cases of wide-neck aneurysms (one at the basilar artery tip and the other at the A1-A2 junction), in which we performed endovascular therapy of Y-stent-assisted coiling using the LVIS Jr. stent.

Case 1

A 54-year-old woman was referred to our hospital for the treatment of an unruptured intracranial aneurysm that was incidentally found on a headache workup. Magnetic resonance angiography (MRA) showed a large wide-neck aneurysm at the basilar artery tip. Endovascular therapy was planned, and we considered the need of a stent-assisted technique. Accordingly, she was given dual antiplatelet therapy (aspirin 100 mg and clopidogrel 75 mg) 10 days before the treatment and her platelet-aggregation inhibition was tested 1 day before the treatment with VerifyNow® System (Accumetrics, San Diego, CA, USA). The endovascular surgery was performed via the right femoral artery under general anesthesia and confirmed the basilar artery tip aneurysm measuring approximately 14.7 × 12.0 mm, with a

7.3-mm neck (Figure 1A). A 6-French guiding sheath was inserted into the left vertebral artery. In advance, a 0.010-inch microcatheter tip was put at aneurysmal sac to perform the coiling with this jailed catheter. An attempt succeeded in advancing the 0.017-inch microcatheter along a microguidewire toward the right posterior cerebral artery (PCA) for the LVIS Jr. stent deployment. A 3.5 × 28 mm LVIS Jr. stent was deployed from the right P1 to the basilar trunk, partially covering the aneurysmal neck. Next, the 0.017-inch microcatheter went through the first stent strut (trans-cell technique) and went toward the left PCA along a microguidewire. After that, the second 3.5 × 23 mm LVIS Jr. stent was deployed from the left P1 to the basilar trunk, creating a Y-stent configuration (Figure 1B). The aneurysmal coiling was achieved via the jailed microcatheter without coil protrusion into the parent arteries (Figure 1C). The patient was discharged with no apparent neurological deficits. She underwent follow-up angiography 90 days after the treatment, which showed complete obliteration of the aneurysm without in-stent stenosis (data not shown).

Figure 1 Case 1. Digital subtraction angiogram showing the large aneurysm (A). Y stent configuration with the LVIS Jr stents (B). Post operative angiogram showing complete obliteration of the aneurysm with good patency of parent arteries (C).

Case 2

A 67-year-old man underwent a complete brain checkup, which resulted in an MRA demonstrating an anterior communicating artery (ACoA) aneurysm. He was referred to our hospital, and endovascular therapy was planned. Dual antiplatelet therapy (aspirin 100 mg and clopidogrel 75 mg) was preloaded, and we checked to verify that there was sufficient platelet-aggregation inhibition before the treatment with the VerifyNow® System. The endovascular surgery was performed via the right femoral artery under general anesthesia and a preoperative angiogram revealed a left A1-A2 junction aneurysm measuring approximately 6.0 × 5.2 mm, with a 5.6-mm neck (Figure 2A). A 6-French guiding sheath was inserted into the left internal carotid artery. Subsequently, a 0.010-inch microcatheter tip was inserted to the aneurysmal sac to perform the coiling with this jailed catheter. The aneurysmal neck was mainly on the left A2. Therefore, we advanced the 0.017-inch microcatheter along a microguidewire to the left A2 and deployed a 2.5 × 17-mm LVIS Jr. stent while pulling back the microcatheter to the left A1. During the coiling after this deployment, the coil loop protruded into the right A2 lumen. We were concerned about the possibility of an infarction due to thrombus formation and, therefore, decided to perform rescue stenting to attach the coil loop to the vascular wall. Then, the 0.017-inch microcatheter was advanced to the right A2 with the trans-cell technique, and a 2.5 × 13 mm LVIS Jr. stent was placed creating a Y shape (Figure 2B). The contrast was no longer filled into the aneurysmal sac, and the parent artery patency was good (Figure 2C), so we finished. The patient recovered from anesthesia without any problems; however, postoperative computed tomography showed subarachnoid hemorrhage. There was a complication of hydrocephalus, and the patient needed a ventricle-peritoneum shunt. He subsequently recovered and was discharged

with no remarkable symptoms.

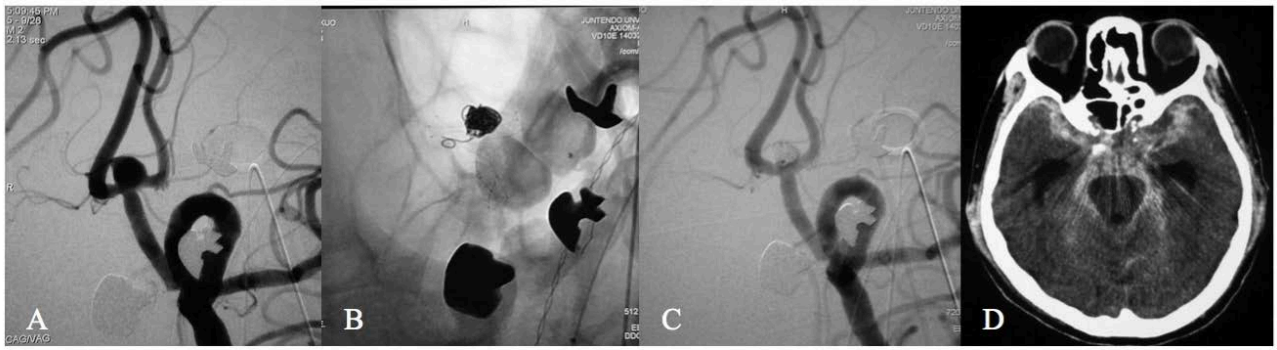

Figure 2 Case 2. Digital subtraction angiogram showing the left A1-A2 junction aneurysm (A). The rescue stenting with Y shape deployment against the protruded coil into the right A2 lumen (B). Post operative angiogram showing obliteration of the aneurysm with good patent A2s. Both A1-A2 junction morphologies are straightened measurably (C). Post operative computed tomography showing subarachnoid hemorrhage with inferior horn dilatations (D).

Discussion

In the past two decades, the endovascular therapy of intracranial aneurysms has progressed remarkably. In the beginning, coil embolization of aneurysms was simply done with bare platinum coils. However, this technique was not possible for wide-neck aneurysms because the spiral shape coils could not go into these aneurysms adequately and could possibly protrude into the parent arteries. Therefore, over the years, several techniques with vascular reconstructive devices have been developed to treat wide-neck aneurysms. They include the evolution of single and dual balloon remodeling, aneurysm neck bridging with single intracranial, Y or X configuration, and cross-court stent-assisted embolization.[1-4] Despite all of these advances, wide-neck aneurysms arising at the vessel terminal of the bifurcation origin represent a subset of lesions that remain challenging for any of these treatment modalities.[5] In these terminal-type aneurysms, the blood flows into the aneurysm neck directly from the opposite side, and constant hemodynamic forces directly attack the aneurysm internally, enabling surgeons to achieve complete occlusion. To treat these intractable aneurysms, tight coil packing with stronger vascular reconstructive devices is needed. Recently, the stent-assisted technique is often used to treat terminal-type aneurysms. Since the first description of stent-assisted coil embolization, the Enterprise stent (Cordis Neurovascular, Miami, Florida, USA) and the Neuroform stent (Stryker Neurovascular, Fremont, California, USA) have been most commonly used. The Enterprise stent can be delivered through a 0.021-inch microcatheter, but when surgeons put this stent in tortuous vessels, they are often apprehensive about the kinking or stent apposition because of the closed-cell characteristics. And this stent can only be used for 2.5 to 4-mm diameter vessels. On the other hand, the Neuroform stent can adequately handle these problems. This stent is the open-cell type, therefore can fit into and navigate through tortuous vessels and be deployed in vessels as small as 2 to 4.5 mm in diameter. However, a 0.027-inch microcatheter is needed to deliver the stent, so the trackability is undesirable. The LVIS Jr. stent can effectively take care of the disadvantages of both of these stents. As it is named, this stent can be delivered with a 0.017-inch low-profile microcatheter, therefore trackability is good. The LVIS Jr. stent resists comparable flexing for a braided structure. Moreover, when surgeons use the trans-cell technique, the mobility of the woven wire is so good that it is relatively easy to cross the microguidewire or the microcatheter. Thus, its advantages are remarkable compared with other devices.

We have reported the short-term results and technique for the Y-stent-assisted coil embolization of unruptured wide-neck intracranial aneurysms, using the LVIS Jr. stent. In Case 1, we achieved a good outcome using the

remarkable advantages of the LVIS Jr. stent. However, the patient in Case 2 suffered a subarachnoid hemorrhage and other severe complications. Several causes were considered. We deployed the second stent as rescue stent to keep the right A2 lumen patent against the protruded coil. The right A2 lumen diameter was slightly less than 2 mm; therefore, there might have been excessive stress on the vessel. Vascular morphological changes after LVIS Jr. stent placements for ACoA aneurysms have been reported.[6]

In Case 2 in the present report, the parent arteries were straightened measurably after the deployment of the LVIS Jr. stents (Figure 2A and C). The stent provided enough radial force to change the vascular morphology of the parent artery despite its smaller diameter. These morphological changes can pull out the origin of the perforators and may cause bleeding. On the other hand, Chung et al. have reported that the deployment of Enterprise stent in small arteries (<2 mm in diameter) was safe and resulted in good patency.[7] The vessel diameter limit of the LVIS Jr. stent deployment is not known precisely, and more experience with a larger number of cases is warranted.

Conclusions

We have reported two cases of a wide-neck aneurysm treated with the LVIS Jr. stent. This device offers a new option for the treatment of wide-neck aneurysms, with clear advantages over the currently available intracranial stents. A larger series and long-term results are needed to confirm the applicability, durability, efficacy, and safety of this stent.

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アトピー性皮膚炎患者唾液のストレスマーカーの検討

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要約：【目的】成人のアトピー性皮膚炎(AD)ではストレスによる掻破が問題となっている。痒みとストレスは密接な関係があるとされているにもかかわらず客観的な指標がないため、主観的な評価が主体である。そこで我々は簡便に採取できる唾液に注目し、ADの重症度や患者のストレスの程度をどの程度唾液中のストレス蛋白が反映するかを検討した。【方法】2015年4月から12月まで島根大学皮膚科を受診したAD患者51名を対象に、重症度(SCORAD)、新版STAIによるストレス評価、新版TEGⅡによる性格評価、生活の質（DLQI）の評価を行った。同時に唾液を採集して、唾液中のクロモグラニンA(CgA)、アミラーゼ 、コルチゾールの測定した。【結果】AD 患者の蛋白あたり唾液中 CgA 値は SCORAD と相関していた（R=0.458、p<0.001)。コルチゾール、アミラーゼ値とSCORADの相関関係はみられなかった。SCORADはDLQIと相関していた（R=0.390、p＝0.006)。また，蛋白あたり唾液中CgAは生活の質の調査であるDLQIとの相関関係を認めた（R=0.393、p＝0.004)。不安の調査STAI、性格検査のTEGⅡ、生活の質のDLQIの間は相関関係を認めた。【結論】重症なAD患者ほどより高いストレス状態にあることが示唆された．AD患者の性格と不安に関連を認めた。

キーワード： 唾液　クロモグラニンA　コルチゾール　アミラーゼ　重症度　ストレス

はじめに

アトピー性皮膚炎は慢性難治性の湿疹を呈し、痒みを伴うことが特徴である1)。その悪化因子は様々であるが特に成人ではストレスによる掻破が問題となっている。ストレスとは、外部からのさまざまな刺激（ストレッサー）によって自分の身体や心に負荷がかかり、「歪み」が生じ、様々な身体への不調を引き起こす原因として重要である。「病は気から」の言葉通り、比較的古くから、疾病と精神との深い関わり合いが知られている。皮膚疾患においても、その病勢が患者の精神状態に大きく左右される例が少なくない2)。ストレスの評価の多くは主観的であるため、客観的に評価できるストレスマーカーが望まれている。唾液は非侵襲的に採取できる 検体として，口腔特有の疾患診断だけでなく3-4)，全身疾患診断の検体として注目されており5−7)。唾液中のクロモグラニンA（ChromograninA：CgA）8)、コルチゾール(hydrocortisone)9-10)、アミラーゼ(Amylase) 11)は精神的ストレスマーカーとして用いられている。

CgAは副腎髄質のクロマフィン顆粒中から分離される酸性の糖蛋白質であり、血中のカテコールアミン類の分泌を反映することから、交感神経-副腎髄質(SAM)系の活動を示すマーカーの一つである。CgAは顎下腺導管部に存在し、自律神経刺激により唾液中に放出されることから、唾液CgAは精神的ストレスの新しい指標として注目されている8)。コルチゾールは、副腎皮質から分泌される主要な糖質ステロイドで、糖代謝をはじめ、蛋白質や脂質代謝にも関与し生体の恒常性を保つ上で免疫系，血管系，中枢系 に対して様々な生理的作用を有し，心理的・身体的な健康状態を考える上でも重要なホルモンである 9)。 コルチゾールはストレスを感じると多量に分泌され，唾液中のコルチゾールはアトピー性皮膚炎のSCORAD と相関が見られている 10)。唾液中のアミラーゼは，ストレスを受けることによる 交感神経系の直接的な作用の一つとして分泌すると考えられている11)。交感神経系の新しい指標として、不快な刺激では唾液アミラーゼ活性が上昇

し，快適な刺激では逆に低下することを見出し，唾液アミラーゼによって快適と不快を判別できる可能性があることを示しされている12-13)。

以上より我々は簡便に採取できる唾液に注目し、アトピー性皮膚炎の痒みの自己評価やSCORAD、相関やストレスのタイプ、治療反応性との相関性を探索的に検討することにより客観的バイオマーカーを創出し活用することを研究の目的とする。

実験方法

1.被験者

2015年4月から2015年12月まで,島根大学医学部皮膚科を受診したAD患者のうち同意の得られた５１名を対象とした。男性29名、女性22名。年齢16-57歳、平均年齢32. 2歳であった。得られた患者の個人情報については符号化した後、解析に用いた。

2.観察、検査の方法

①臨床症状、皮疹のSCORAD、血清LDH、血清TARC 、抗原特異的IgE。

②患者受診時に次の質問票への記入を依頼する。不安度の客観的評価法新版STAI、性格調査（新版TEGⅡ）、生活の質DLQI調査。

③唾液採集方法：サンプルを採集前はカフエインや砂糖、酸性の食物を口に入れない。採集までの２０分間は乳製品を避ける。４５分以内は歯を磨かない。１時間は食事を避ける。１２時間はアルコールを避ける。２日以内は歯科医による処置を受けない。以上の条件の下、採集前に３回口を水で濯ぎ、後１０分待ってから口の中に唾液を留め、頭を傾け、唾液を容器に垂らします、２ｍｌチューブの半分以上が得られるまでこれを繰り返した。唾液採集キットを渡して、受診時に回収した。

3.唾液測定内容

採集した唾液は遠心分離（3000 rpm、15分）して、分離後、回収された唾液を小ポリプロピレンチューブなどに移し、測定まで−20℃で冷凍保存した。

① CgAの濃度測定は酵素免疫測定法（EIA）（YK070 Human Chromogranin A EIA株式会社矢内原研究所）を用いた。

②コルチゾールの濃度測定は(SALIMETRICS,Corticosterone ELISA KIT ）を用いた。

③アミラーゼの濃度測定は唾液アミラーゼモニター（１２S001579,ニプロ株式会社）を用いた。

アンケート調査内容

アンケート調査はAD患者外来診療時に次の3項目について行った。

①STAI（新版State Trait Anxiety Inventory:STAI）状態―特性不安性格調査14)。STAIは状態不安と特性不安に分けられ、状態不安は自律神経の興奮などを伴う一時的、状況的な不安状態を示す15)。特性不安はストレス状態に対して状態不安を喚起させやすい傾向であり、比較的安定状態した個人内特性と捕らえられる16)。状態不安尺度と特性不安尺度の２つの尺度を同時に実施した。

②TEG（Tokyo university Egogram 新版TEGⅡ）は個人のパーソナリティの各自我状態同士の関係と、外部に放出している心的エネルギーの量を５つの棒グラフで表し、性格特性と行動パターンをみるもの。新版 TEGⅡの５尺度は、CP(Critical parent)、NP(Nurturing parent)、A(Adult)、FC(Free child)、AC(Adapted child)の５つの自我状態に対応している17)。各尺度の高低の関係により、ある人格特性を理解することが可能である。各自我状態は、いい悪いで言えるものでなく、長所ととらえられるところと短所ととらえられるところと両面をもっているとされている。

③ DLQI は(Dermatology Life Quality Index)はさまざまな皮膚疾患の QOL を測定、比較することができ、項目数の少ない尺度である。全 10 項目、「症状,感情,日常活動,レジャー,仕事,学校,人間関係,治療」の６つの尺度から構成されている。それぞれの下位尺度得点と総合得点（0-30 点）を求めることができる 18)。

統計解析

実験結果は平均値±標準偏差(mean±SD)で示す。解析ソフトは R, version 3.2.2 (The R Foundation for Statistical Computing, Vienna, Austria)で行った。相関を Pearson’s product-moment correlation coefficient にて求め、有意水準は 5%以下とした。

結 果

51 名患者は厚生労働省の研究班による「重症度のめやす」によると軽症 18 名、中等症 22 名、重症 9 名、最重症 2 名であった。外来患者４８名、入院患者３名であった。各項目について表１に示す。

表１　患者背景（51 名）

診察項目	mean±SD
罹病期間	18.4±10.0　年
SCORAD	33.3±15.6
SCORADobjective	27.0±13.2
TACR(測定できた人 30 名)	1956.8±1868.2 pg/ml
総 IgE(測定できた人 33 名)	9634.7±10517.3 IU/ml

１.唾液中の CgA、アミラーゼ、コルチゾールと SCORAD の相関関係。

AD 患者の唾液中 CgA 値、蛋白で割った値は SCORAD、SCORAD objective と相関していた,図 1(a、b、c、d)。唾液中コルチゾール、アミラーゼ値と SCORAD の相関関係はみられなかった, 図１(e、f、g、h)。

2.AD 患者唾液中の CgA、アミラーゼ、コルチゾールと不安尺度の結果の相関関係, CgA は DLQI と相関していた、図２(a、b), CgA、アミラーゼ、コルチゾールと STAI の相関を認めなかった、図２ (c、d、e、f、g、h)。

3.SCROAD と不安尺度の結果 (STAI、TEGⅡ、DLQI) の相関関係。SCORAD は DLQI と相関していた、図３ (a、b)、SCORAD は STAI との相関を認めなかった、図３ (c、d)。

4. 不安尺度の結果 STAI、TEGⅡ、DLQI の間の一部は相関していた、図４ (a、b、c、d、e、f、g、h、i、j、k)。

表２　相関をみとめた項目

項　目	有意差	
CgA と SCORAD	R=0.419	P=0.003
CgA/protein と SCORAD	R=0.458	P<0.001
CgA と DLQI	R=0.347	P=0.013
CgA/protein と DLQI	R=0.393	P=0.004
SCORAD と DLQI	R=0.390	P=0.006
STAI 状態不安と TEGⅡ-FC	R=-0.303	P=0.031
STAI 特性不安と TEGⅡ-CP	R=-0.286	P=0.042
STAI 特性不安と TEGⅡ-FC	R=-0.424	P=0.002

STAI 特性不安と TEGⅡ-AC	R=0.474	P<0.001
STAI 特性不安と DLQI	R=0.458	P<0.001

考察

ストレスには肉体的、物理的ストレスと心理的ストレスが考えられているが、これらを明確に区別することは困難であり、たとえば18歳前後にAD患者数が増加することは受験という精神的ストレスに加え、受験勉強に伴う睡眠不足、慢性の疲労などの肉体的ストレスが増悪因子として考えられている19)。AD患者は心理社会的負荷に対して、適切に対処できない20）との報告もあり、痒みに対する掻破をくり返すうちにこれが心理社会的負荷に対する行動に一つに変化していった可能性が推察される21)。重症のADではitch-scratch cycleとは別の、stress-scratch cycle22）ができており、心理社会的負荷のもとでは行動異常として嗜癖的掻破行動が増強し、この cycle が回転すると考えられ、このstress-scratch cycle に対するアプローチが治療上非常に重要であると言える 23-24)。このようにストレスの原因としては様々なものが考えられ、ADの増悪因子にストレスが挙げられているが、どのようなストレスがどの程度負荷されるとADがどの程度悪化するのかは不明である。

近年、唾液中のストレスバイオマーカーについて解析がすすめられている。急性痛は精神的ストレスよりも身体的ストレスの要素が大きいため、急性痛では唾液CgAは増加しないとされており25)、恐怖感情 に対しては唾液中CgA濃度が増加すると報告されている26)。また、コルチゾールが身体的ストレスに対して反応を示すのに対し、CgAは心理的ストレスに対して反応を示す特性があるとされている27）。そこで我々は、簡便に採取できる唾液に注目し、ADのSCORADや患者のストレスの程度をどの程度唾液中のストレス蛋白が反映するかを検討した。過去の報告では、初診AD群は初診非AD群、再診AD群にくらべ有意に唾液中CgA量が高値であるとの報告28)やADの唾液中コルチゾール量は高値で重症度と相関するとの報告10)などがみられ、ADの唾液中アミラーゼ量についての報告はなく、統合失調症の患者で高値であることからストレスとの関連が考えられている 29)。我々の結果は診察時に随時にとった唾液中 CgA とアトピー性皮膚炎の SCORADとは相関したが、唾液中コルチゾール値、唾液中アミラーゼ値とは SCORAD は相関しなかった。身体的なストレス要因と考えられるADのSCORADが心理的なストレスと相関することになり、ADにおけるストレスを考える上で興味深い。ただし、コルチゾールは日内変動があることが周知の事実で有り、このために相関がみられなかった可能性は十分考えられる。日常臨床においては、診察時に検査を行うことがほとんどであるため、ストレスを検討するにはCgAがより有用である可能性が考えられた。CgAが著明高値を示した1症例についてであるが、この患者は入院するくらい重症なAD患者あったためと考えられる。CgAはDLQI とも相関がみられており（図2a,b)、重要な唾液のストレスマーカーであることが示唆される。

ストレスや不安に対しての評価はこれまで各種質問紙による検討がなされてきた。今回我々も質問紙による AD 患者の不安や性格の評価を行ったが、残念ながら唾液中のストレスマーカーとの相関は認められなかった。しかし AD 患者に特有な傾向がみられ性格の調査で「母親的親の心」や「自由な子どもの心」が高い性格だと状態不安（その時の不安）が少ない傾向があり、「順応した子どもの心」はが高い性格だと特性不安（不安の感じやすさ）が高い傾向がみられた。これらの解析は患者指導にも有用にはたらく可能性があると考える。AD患者で順応した子どもの心が高いとの報告30)があり、今回の傾向もそのことが示唆されさらに不安との関連が判明した。

今回の我々の検討にて簡便に採取できる診察時の唾液にて AD 患者の重症との関連を客観的に示した点は医学的重要性が高く、さらに治療介入による唾液中CgA値の変化や、他の炎症性疾患患者への応用など臨床的発展が期待できる。さらに患者のストレスマネージメントに応用出来ると考えられるが、まず何がストレスとなっているのかの理解が必要である。この問いが簡単なようで、真の理由が判明することは稀である。日常の問診の中にヒントが隠れていることが多く、その為にも問診のテクニックが必要なところである。このようなストレスマネージメントの前提には、良好は医師-患者関係

を確立することが基本であり、筆者らのアンケート調査においても、自由意見を記述した 189 名中 28 名（14.8%）がその点を強調していた 31)。今回の唾液による客観的なストレスマーカーの解析が今後のストレスマネージメント、ストレスコーピングの有用なツールとなると考え報告する。

まとめ（結論）

重症な AD 患者ほどより高いストレス状態にあることが示唆された。簡便な唾液による CgA 測定が患者のストレスの客観的な評価に有用と考えられる。AD 患者の性格と不安に関連を認めたが、唾液のストレスマーカーとの相関は認めなかった。

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利益相反

本研究に関し開示すべき利益相反はない。

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図の説明

図１ CgA、アミラーゼ、コルチゾールとSCORADの関係

(a) CgA とSCORADの間は有意差があって、R=0.149、p＝0.003

(b) CgA と SCORAD objective の間は有意差があって、0.349、p＝0.013

(c) CgA/protein と SCORAD の間は有意差があって、R=0.458、p<0.001

(d) CgA/protein と SCORAD objective の間は有意差があって、r=0.385、p＝0.006

(e) アミラーゼと SCORAD は有意差がなかった, R=-0.161、p＝0.267

(f) アミラーゼと SCORAD objective は有意差がなかった,R=-0.1411、p＝0.329

(g) コルチゾールと SCORAD は有意差がなかった,R=0.138、p＝0.345

(h) コルチゾールと SCORAD objective 有意差がなかった,R=0.125、p＝0.389

図２　CgA、アミラーゼ、コルチゾールと不安尺度 DLQI、STAI の結果の関係

(a) CgA と DLQI の間は有意差があって、R=0.347、p＝0.013

(b) CgA/protein と DLQI の間は有意差があって、R=0.393、p＝0.004

(C) CgA/protein と STAI 状態合計は有意差がなかった、R=0.085、p＝0.551

(D) CgA/protein と STAI 特性合計は有意差がなかった、R=0,087、p＝0.545

(E) アミラーゼ/protein と STAI 状態合計は有意差がなかった、R=0.111、p＝0.436

(F) アミラーゼ/protein と STAI 特性合計は有意差がなかった、R=0.175、p＝0.218

(G) コルチゾール/protein と STAI 状態合計は有意差がなかった、R=-0.174、p＝0.220

(H) コルチゾール/protein と STAI 特性合計は有意差がなかった、R=0.156、p＝0.273

図３　SCROAD と不安尺度の結果 DLQI 、STAI の関係

(a) SCORAD と DLQI の間は有意差があって、R=0.390、p＝0.006

(b) SCORAD objective と DLQI の間は有意差があって、R=0.302、p＝0.033

(c) SCORAD と STAI 状態合計は有意差がなかった、R=0.049、p＝0.737

(d) SCORAD と STAI 特性合計は有意差がなかった、R=0.029、p＝0.844

図４ 不安尺度の結果 STAI と TEGⅡ、STAI と DLQI の間の関係

(a) STAI 状態 A と TEGⅡ-NP は有意差があって、R=-0.349、p＝0.012

(b) STAI 状態合計と TEGⅡ-FC は有意差があって、R=-0.303、p＝0.031

(c) STAI 特性 P と TEGⅡ-AC は有意差があって、R=0.572、p<0.001

(d) STAI 特性 A と TEGⅡ-NP は有意差があって、R=-0.369、p＝0.008

(e) STAI 特性 A と TEGⅡ-FC は有意差があって、R=-0.551、p<0.001

(f) STAI 特性合計と TEGⅡ-CP は有意差があって、R=-0.286、p＝0.042

(g) STAI 特性合計と TEGⅡ-FC は有意差があって、R=-0.424、p＝0.002

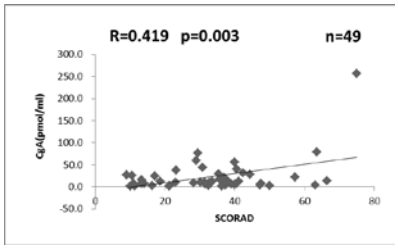
(h) STAI 特性合計と TEGⅡ-AC は有意差があって、R=0.474、p<0.001

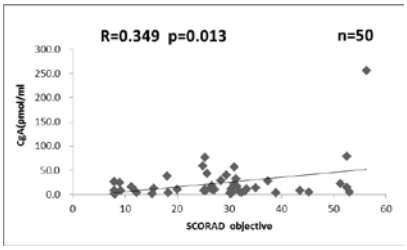
(i) STAI 特性 P と DLQI は有意差があって、R=0.456、p<0.001

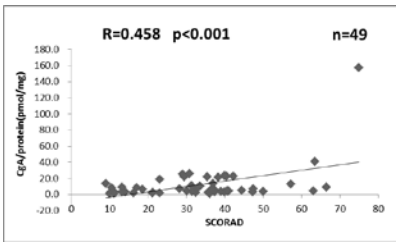
(j) STAI 特性 A と DLQI は有意差があって、R=0.345、p＝0.013

(k) STAI 特性合計と DLQI は有意差があって、R=0.458、p<0.001

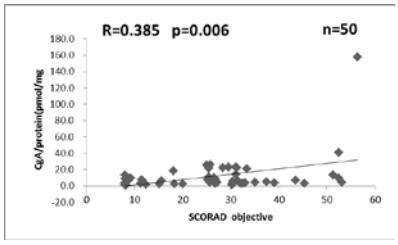
図1　a　　b　　c

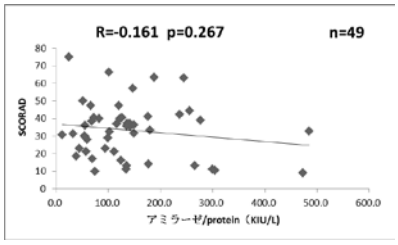


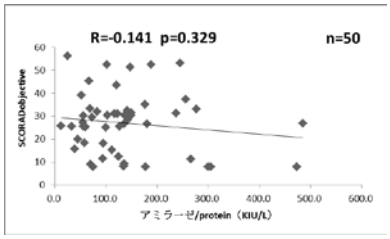




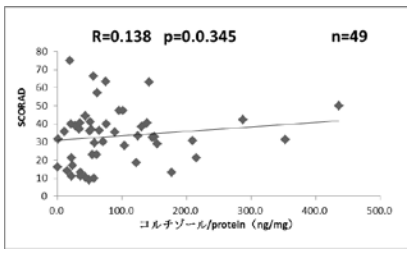
d　　e　　f







g　　h



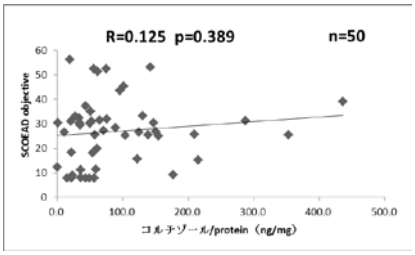
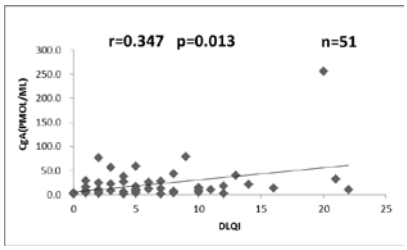
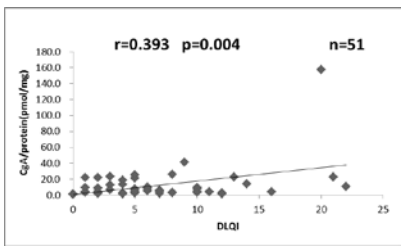
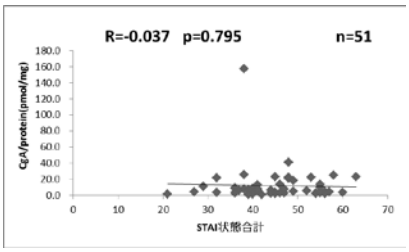


図2　a　　b　　c







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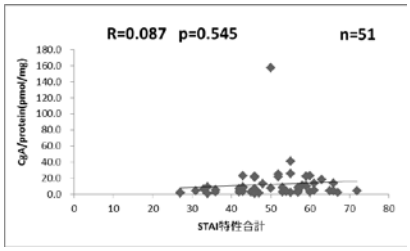

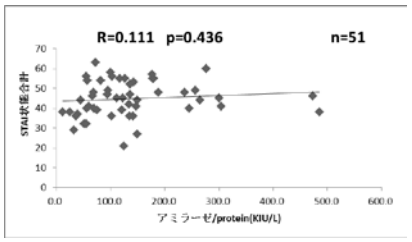

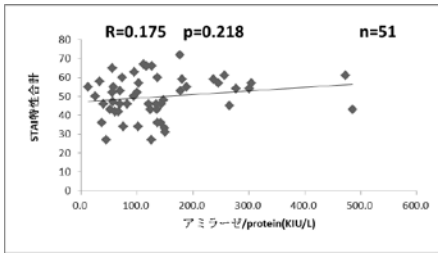

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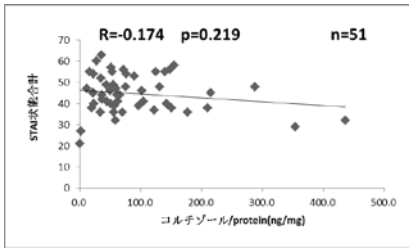

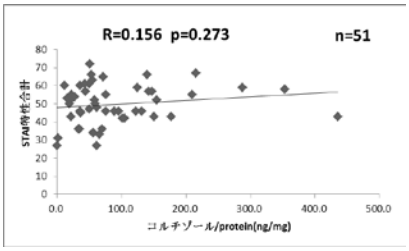

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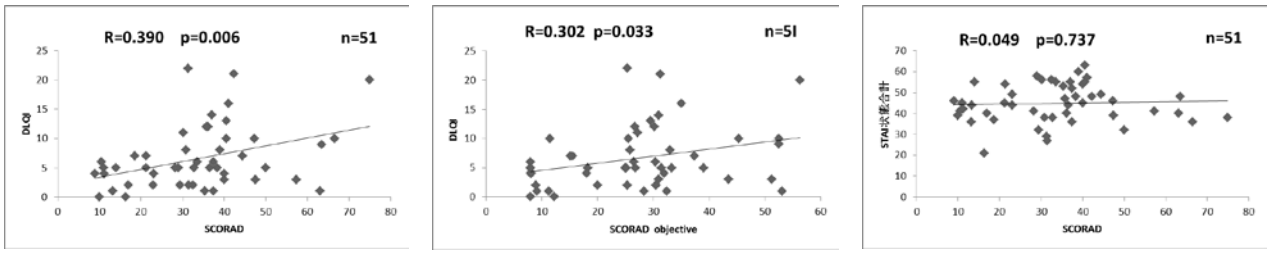

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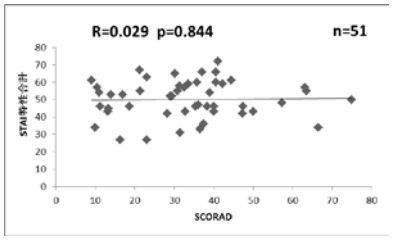

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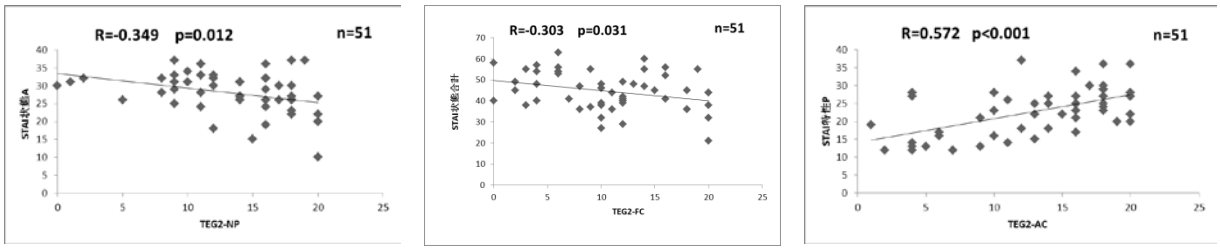

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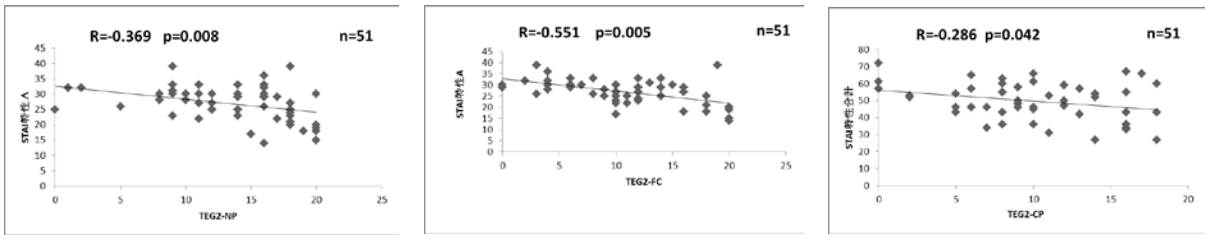

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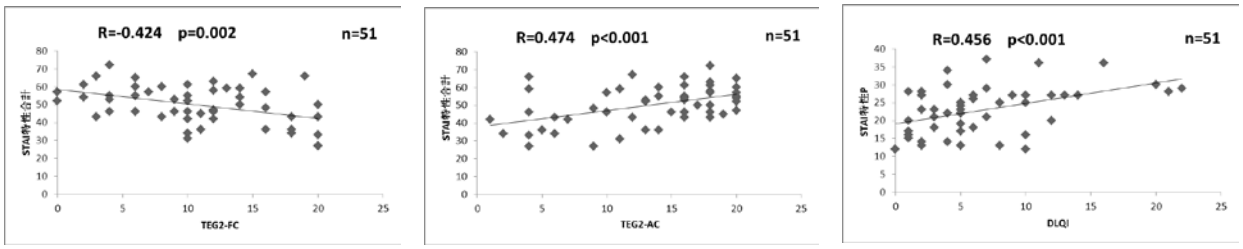

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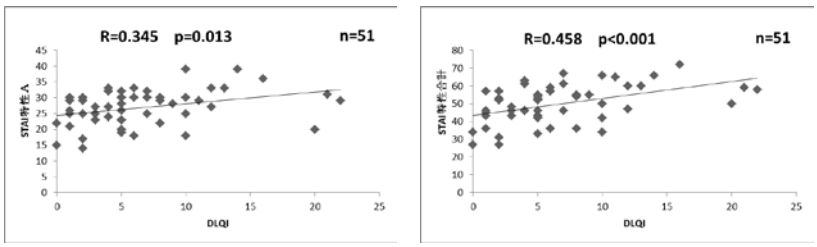

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作成日：2016年2月29日

《一年間の研究業績》

■学会、研究会、報告会等での発表(在学会、研究会、报告会等的发表，请使用发表**原文的语言**填写)

演　　題(研究题目)	アトピー性皮膚炎患者唾液のストレスマーカーの検討		
学　会　名(学会名称)	日本皮膚科学会第 130 回山陰・第 26 回島根合同開催地方会		
開　催　日(召开日期)	2016 年 2 月 28 日	開　催　地(召开地)	出雲市
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共同演者名(共同演讲者)	金子　栄、森田　栄伸		

演　　題(研究题目)			
学　会　名(学会名称)			
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学　会　名(学会名称)			
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形　　式(发表形式)	☐口演発表（口头报告）☐ポスター発表（墙报展示）	☐英語☐日本語☐中国語	
共同演者名(共同演讲者)			

The Detail of the En-bloc technique and Prognosis of Spleen-preserving Laparoscopic Distal Pancreatectomy for Pancreatic Cancer

En-bloc 切除の技術と膵臓癌に対して腹腔鏡下膵体尾部切除の予後評価

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Abstract:

Background: Although Laparoscopic spleen-preserving distal pancreatectomy surgery is more and more popular. The reports about the En-bloc technique used for pancreatic cancer were still rare. The aim of our study was to illustrate the detail of the spleen-preserving En-bloc technique as while as the short-term, long-term outcomes. **Methods:** Describe the detail of the En-bloc technique with pictures. Evaluate the prognosis of successive 19 cases who underwent the laparoscopic distal pancreatectomy (LDP) surgery. **Results:** There were 11 cases that underwent spleen-preserving LDP while 8 cases underwent spleen-resecting LDP. The average surgery time was 208±48 minutes, the average blood loss volume was 203 ± 245 ml.1 case transferred to open surgery because of severe adhesion. The complication rate was 45.5% (n = 5) in short-term after surgery. Pancreatic fistula rate was 36.3% (n = 4). No lethal case occurred. The average diameter of the tumor was 35 ± 10 mm. Average number of the lymph nodes obtained was 17.5 ± 7.2.All the cutting edges were negative. Survival rate of the patient after 1, 3, 5 year is 64.7%, 52.9% and 41.2%. These records showed no statistical significance compared with spleen-resecting LDP and ODP surgeries. Conclusions: the En-bloc spleen-preserving LDP can be performed by experienced surgeons. This surgery has good short-term and long-term outcome.

Key Words:

Spleen-preserving, laparoscopic distal pancreatectomy, pancreatic cancer

Introduction:

In the past 20 years, laparoscopic pancreatectomy surgery has been recognized and performed gradually from diagnostic laparoscopic exploration, specimen biopsy to distal pancreatectomy and pancreato-duodenectomy (1). Because the procedure of laparoscopic distal pancreatectomy (LDP) was not very complex, the number of cases underwent this surgery raised quickly for benign and low-grade malignant disease.

Depending on the Japanese General Rules for the Study of Pancreatic Cancer , We designed an enbloc spleen-preserving LDP procedure which remove the Gerota facia, Tolt facia and the distal pancreas as a whole and resect 1st, 2nd station lymph nodes. Spleen-preserving LDP against pancreatic cancer may be still controversial, until now there hasn't been any report from a single centre about the long-term prognosis and the standard En-bloc LDP procedure of the surgery. Our aim is to describe the detail of the standard En-bloc technique and to evaluate the short-term and long-term prognosis compared with the previous studies (3-6) about ODP.

Materials and methods:

From the year 2007 to 2010, there were 60 patients underwent DP surgery. Among them, 28 cases underwent LDP surgery; 32 cases

underwent ODP surgery. 19 cases were pancreatic cancer in LDP surgery group. Before the year 2002, the indications of LDP were benign diseases. After 2002 LDP was indicated both in benign and malignant diseases. All the patients' medical records and pathology results were reviewed.

2.1. *Ethics, consents and permissions*

The demerits of LDP against pancreatic cancer were the high requirements of surgical skills and the uncertain outcomes. The merits of LDP were the micro-invasive effects leading to fast recovery.

This retrospective study was approved by Peking University Ninth School of Clinical Medicine ethics committee. Patient records were de-identified prior to analysis. All the patients signed informed consents before surgery.

2.2. The surgical procedure of en-bloc LDP

We have 3 principles in the concept of En-bloc spleen-preserving LDP surgery. Firstly is to dissect from the Gerota fascia to Tolt fascia exposing the left kidney, left renal vein, left adrenal vessels, left adrenal gland. En blos dissect the Gerota fascia and Tolt fascia and distal pancreas. Secondly Dissect lymph nodes and ganglions along the celiac trunks while resect the lymph nodes and ganglion along the superior mesentery artery (SMA). Thirdly if the spleen and the left gastro-epiploic vessels were not invaded, dissect the spleen vessels, but preserve the spleen.

The detail of the technique is depicted as follows.

The patient is placed in a lithotomic position. We insert 10-mm trocars in the umbilicus and right mid-clavicle line below the costal margin separately, double 5-mm trocars in the left upper quadrant of abdomen. After dissect the greater omentum, divide the mesocolon transversum from the Gerota fascia. Identify the inferior border of the pancreas.

Dissect from Gerota fascia to Tolt fascia exposing left kidney, left renal vein, left adrenal gland and IMV with En-bloc method from lateral to medial. Retract the pancreas from dorsal side to ventral side. Expose the junction of the spleen vein and SMV from the dossal side of the pancreas. We mobilized the SMA, resected the lymph nodes and celiac ganglion group II at the left side of SMA.

We dissect the parenchyma of the pancreas at the root of spleen vein. After that, ligate the spleen vein and spleen artery at the root. Continue to resect the lymph nodes and celiac ganglion group II at the left side of SMA. Preserve right half of the celiac ganglion group II at this place. Dissect adipose tissue upward to the cephalic side. Expose the celiac trunk, resect the lymph nodes and celiac ganglion group I at root of celiac trunk. Preserve right half of the celiac ganglion I. Then move to the left. Skeletonize the left adrenal gland and resect the adipose tissue and lymph nodes around it.

Finally, at the tail of the pancreas, ligate and dissect the spleen vessels, preserve the gastro-epiploic vessels and short gastric vessels.

After these procedure, the common hepatic artery, left gastric artery, celiac trunk, SMA, left adrenal gland and its vessels, left kidney, left renal vein are Exposed. The En-bloc distal pancreatectomy is finished. At last we should close the pancreatic duct, dislodge the specimen and leave a drainage at the surgical region.

2.3. *Data collection and statistic analysis*

To analyse the complications after surgery, we adopt Clavian-Dindo classification method (7). To analyse the pancreatic fistula we adopt International Study Group of Pancreatic Fistula classification method (8).The definition of spleen infarction was that the regional or total spleen is not enhanced by contrast-enhanced CT. The criteria of discharge was that the complications of the patient was stable, no

analgesia was taken and the patient could accomplish daily activity. The follow up items after discharge included routine test, tumor markers (CEA, CA199), contrast-enhanced CT or MRI according to NCCN guideline(9).

Statistic Analysis: Categorical variables were demonstrated as quantity or percentage. To compare between groups, we use Fisher test or chi-square. Successive variables were demonstrated as Mean± SD. To compare them, we use t test. Survival duration started from the date of the surgery. Recurrence-free survival curve was depicted by Kaplan–Meier method. When we evaluated the Recurrence-free survival time, we included the Recurrence-free lethal cases. SPSS (version 19.0.2; SAS Institute Inc., Cary, NC) software was used in statistic analysis.

Results:

Among the 19 pancreatic cancer patients who underwent LDP. 12 were male, 7 were female. Average age was 63±7.4 years. Average BMI was 24.7 ± 3.4 kg/m2. Anesthesia risk score (ASA score) was 2.3. No patients underwent neo-chemotherapy before surgery. There is 11 spleen-preserving LDP cases and 8 spleen-resecting LDP cases. Average surgery time was 208 ± 48 minutes. Average blood loss was 203 ± 245 ml. 1 case converted to ODP because of severe adhesion between greater omentum, transverse colon and intestine. There was no statistical significance in surgery time between spleen-preserving LDP group and the spleen-resecting LDP group (202 ± 51 vs 216 ± 35 minutes; P = 0.46). There was no statistical significance in blood loss too (184 ± 64 vs 208 ± 78 ml; P = 0.56).

The overall incidence of complication is 45.5% (n = 5). The incidence of pancreatic fistula was 36.3% (n = 4). There was no statistical significance in complication rate between the two groups (45.5%, n = 5 vs 37.5%, n = 3; P =0.96). All the patients were discharged within 30 days. There were 3 cases of grade IIIa complications. 2 cases underwent percutaneous catheter drainage under the ultrasound scan. 1 cases underwent ERCP to definite the pancreatic fistula. 2 cases were diagnosed spleen infarction. 9 patients were not spleen infarction. 1 patients didn't take CT examination after surgery.

All the patients suffered from spleen infarction underwent conservative treatment, and all were cured without spleenectomy. The average length of stay (LOS) was 16 ± 5 days. There was no statistic significance between the spleen-preserving and spleen-resecting LDP groups (17 ± 7 vs14 ± 5 days; P =0.46). The average dimension of the tumor was 35 ± 10mm. The average number of lymph nodes that the specimen contained was 17.5 ± 7.2. There were 10 patients whose positive lymph nodes number ≥ 1. The pathology results were 8 cases of ductal adenocarcinoma, 3 cases of intraductal papillary mucinous adenocarcinoma and one case of Mucinous adenocarcinoma. The surgical margins of all the patients were negative. The final pathology results of the patients were as follows: 1 cases of IA stage (8.5%), 2 cases of IB stage (22%), 2 cases of IIA (8.5%), 5 cases of IIB (57%), 1 of III stage (4%).

Long-term prognosis: The observation period was 5 years after surgery. The average survival duration was 21 months. The survival rate of 1, 3, 5 years after surgery was 64.7%, 52.9% and 41.2% respectively. 6 patients suffered from local recurrence. 1 local recurrent combined with liver metastasis, 2 retroperitoneal recurrent. The average time to recurrence was 14 months. The recurrence free survival rate of 1, 3, 5 years after surgery was 61.6%, 44.1% and 32.3% respectively.

Discussion:

In recent studies (10, 11), the efficacy of radical en-bloc LDP is satisfied for treatment of pancreatic cancer in long-term survival (5 year overall survival was 33%). It is acceptable for treating with pancreatic cancer. The data of our research was from a single centre. The concept of En-bloc LDP was based on R0 resection and enough Lymphadenectomy and ganglion resection.

Why we preserve spleen? Adverse consequences have been observed after splenectomy. These include a greater likelihood of postoperative abscesses (12-14), and most notably a long-term risk of serious post-splenectomy sepsis. The risk of overwhelming

post-splenectomy infection (OPSI) has been estimated to be 1 per 400–500 patient and fatal OPSI to be 1 per 800–1000 patient years (15, 16). While this risk is greatest in childhood, it persists to a lesser degree throughout life (17). In addition, it increases the risk of later myocardial infarction, diabetes, and even cancer (18, 19).

How many types of spleen-preserving LDP surgery in the world? There are mainly two types. One is invented by Kimura (20) who perform spleen-preserving distal pancreatectomy with conservation of the splenic artery and vein. The advantage of this procedure was the low occurrence rate of spleen infarction. The disadvantage was isolating spleen vessels from Tolt facia which not conform to the en-bloc standards, in other hand this procedure is difficult. The other procedure was invented by Warshaw(21) who perform spleen-preserving distal pancreatectomy with resection of splenic artery and vein. The blood flow of spleen after surgery was compensated by left gastro-epiploic vessels and short gastric vessels. Our procedure is similar with Warshaw's procedure except for more extensive retro-peritoneal resection, lymphadenectomy and celiac ganglion resection.

Our study compared with recent studies shows: The number of lymph nodes obtained by LDP was similar with ODP (17.8 vs. 14.5). 100% R0 rate was our most satisfy outcome. The average dimension of the tumor was similar with ODP (35.1 vs. 34.2 mm) too.

The decrease of blood loss during surgery compared with ODP (203 vs. 528ml) was mainly due to amplification of the view and precise manipulate under the laparoscope as well as the increased abdominal pressure.

The en-bloc LDP technique emphasize resecting the Gerota fascia, Tolt fascia and spleen vessels and distal pancreas as a whole to ensure the negative surgical margin. In contrast, in the standard ODP, it didn't need to remove the Gerota fascia and Tolt fascia routinely. It's a controversial topic if we should preserve the spleen. Some study (22) showed that the incidence rate of spleen infarction was 11% to 29%. Till now there hasn't been any guideline support that LDP should combined with spleenectomy.

Distal pancreatic cancers sometimes invade to the lymph nodes and ganglion around the superior mesenteric artery. But totally dissect the nerve plexus around the SMA often results in intractable diarrhea and vomitting. So we preserved part of nerve plexus at the right side of superior mesenteric artery while dissect lymph nodes and ganglions as previously reported (23).

Kim etal (22) reported that there was low incidence rate of lymphatic metastasis at the hilar lienis. Preserving the spleen can avoid the decreasing of immuno-ability and improve the oncological prognosis. All these reports (16-23) support us to preserve the spleen. Till now there hasn't been any re-operate case because of hilar lienis lymphatic metastasis.

It was (6) reported that the average LOS after ODP was 11 ± 7 days. Kooby (3) reported the LOS after LDP was 7 ± 3 days. Because of the different discharge criteria, LOS is difficult to compare. Main reason prolonged LOS is complications (47%), such as pancreatic fistula (39%). The optimized operative technique can reduce the incidence of complication. But these techniques should also be summarized by large number cases of study.

In our study, the prognosis of en-bloc LDP preserving spleen was similar with the reports previously (4, 6, 24, 25). In these reports, the average OS was 13 to 26 months, 5-year survival rate was 19-36%. Till now the reports we searched, it is the first study about the long-term prognosis of standard en-bloc LDP preserving spleen. The limitations of our research were the character of retrospective study and the only 3 types of pathology results. Randomized controlled trials, large number, long-term trial can avoid these disadvantages. But because the incidence rate of distal pancreatic cancer is low, the study is hard to carry out.

Anyway, en-bloc LDP preserving the spleen is safe and effective. The short-term, long-term prognosis is satisfied which supporting this procedure as a treatment for distal pancreatic cancer.

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■学会誌等に発表した論文（投稿中、掲載予定も含む）

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論 文 名 （论文题目）	Regression analysis of the risk factors for postoperative nosocomial infection in patients with abdominal tumors: experience from a large cancer centre in China		
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■学会誌等に発表した論文（投稿中、掲載予定も含む）

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論 文 名 （论文题目）	Evaluation of insulin resistance improvement after laparoscopic sleeve gastrectomy or gastric bypass surgery with Homa-IR: A case control study		
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論 文 名 （论文题目）	Controversy and progress for treatment of acute cholangitis after Tokyo Guidelines (TG13)		
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第 1 著者名（第 1 作者）	Zhipeng Sun	第 2 著者名（第 2 作者）	Bin Zhu
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論 文 名 （论文题目）			
掲載誌名 （登载杂志）			
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Anti-insulin resistance and anti-adipogenic effects of several natural products
天然化合物のインスリン抵抗性および脂肪細胞肥大化に対する抑制効果の検討

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Abstract

Purpose: In this study, the anti-insulin resistance and anti-adipogenic effects of several natural products were investigated in 3T3-L1 adipocytes.

Methods: To investigate anti-insulin resistance and anti-adipogenic effect, 2-deoxy-D-glucose uptake assay and Oil red O quantification assay were performed. Meanwhile, the effects of these compounds on ganglioside GM3 expression and GM3 synthase(GM3S) activity were investigated. To investigate the mechanisms of the compounds which have anti-insulin resistance and anti-adipogenic effects, insulin signal transduction was assessed by western blot analysis using phospho-specific antibodies.

Results: As an inflammatory factor, TNF-α significantly induced glucose and insulin intolerance, and concomitantly, the level of ganglioside GM3 was raised significantly. Our research showed that four compounds and two extracts improved the insulin resistance with enhancing glucose uptake in adipocytes, four compounds and one extract can inhibited the adipogenesis. Tanshinone could decrease the level of GM3, but all the tested products could not inhibit the activity of GM3S.

Conclusions: Two compounds have dual activities, improving glucose uptake and inhibiting lipid accumulation in 3T3-L1 adipocytes. Our findings suggest that these two compounds might be good candidate drugs with great potentialities in the treatment of type 2 diabetes and obesity.

Key Words：Glucose uptake, anti-adipogenesism, type 2 diabetes, obesity, GM3

1. Introduction

Hyperliposis and hyperglycemia are the two strong risk factors for metabolic disorders, including type 2diabetes, obesity, and cardiovascular diseases, and has become a worldwide public health problem (1, 2). 3T3-L1 preadipocytes is very suitable for the study of adipogenesis and hyperglycemia. In our research, anti-insulin resistance and anti-adipogenic effects of ten pure compounds and three extracts were examined.

2. Materials and methods

2.1 Materials

All the compounds were purchased from Sichuan Weikeqi Biological Technology Co., Ltd. 2-deoxy-D-glucose and phloretin were purchased from Wako Pure Chemical Industries Ltd. Glucose cellular uptake measurement kit (Broad range, Fluorometric) was purchased from Cosmo Bio Co., Ltd.

2.2 Cell culture, adipocytes differentiation, induction of insulin resistance and preparation of GM3 synthase

Murine 3T3-L1 preadipocytes were cultured in high glucose-DMEM supplemented with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin at 37℃ in 5% CO_2 incubator. Cells were seeded and grown for 2 days post-confluence, differentiation was induced by adding 0.5mM 3-isobutyl-1-methylaxanthine, 1μM dexamethasone and 1.7μM insulin in high glucose-DMEM. After 72h, the differentiation medium was replaced with maintenance medium containing high glucose-DMEM with 10% FBS and 100ng/ml insulin. About 10 days after the induction of differentiation, ＞95% of the cells had the morphological and biochemical properties of adipocytes. The maintenance medium was changed every 48h until the adipocytes were utilized for experiments.

For induction of insulin resistance, fully differentiated adipocytes were incubated for 96h in maintenance medium

supplemented with 0.1nM human TNF-α (3).

MEF-1-M3GM3S cells were cultured with low-glucose DMEM, supplemented with 10% FBS. After the cells were confluent, cells were washed twice with ice-cold saline, suspended in buffer containing 50mM Tris-HCl (pH 7.5), 150mM NaCl, 10% glycerol and supplemented 1× protease inhibitor, and lysed by sonication 3 times on ice. After removal of cell debris by centrifugation at 1000g for 3min at 4℃, the supernatant was centrifuged at 100,000 xg for 1h at 4℃, the activity of precipitates (microsomal of GM3S) was measured for GM3S activity, then stored at -20℃.

2.3 Glucose uptake assay

Insulin-induced glucose uptake enhancing assay was performed by a fluorescent method with glucose cellular uptake measurement Kit (Cosmo Bio Co., LTD). For enhancing glucose uptake of insulin resistance model of adipocytes, fully differentiated 3T3-L1 adipocytes were incubated in the maintenance medium containing 0.1nM human TNF-α, and meanwhile the natural products were added. After 48h, the maintenance medium was replaced with serum-free medium containing 0.5% BSA and natural products, the cells were starved for 8 hours. Then, the cells were washed 3 times with warm Krebs Ringer Phosphate HEPES(KRPH) buffer, incubated with KRPH containing 2% BSA and 100nM insulin for 20 minutes, and then 1mM 2-deoxyglucose(2-DG) was added. After 20 min, the cells were washed 3 times with cooled PBS containing 200μM phloretin to inhibit further 2-DG uptake. According to the protocol of the Kits, glucose uptake of the cells was measured (4).

For the enhancing glucose uptake of 3T3-L1 adipocytes, fully differentiated adipocytes were treated with maintenance medium containing natural products for 8 hours (5). The following steps were similar to insulin resistance model of 3T3-L1 adipocytes.

2.4 Oil red O staining and quantification

To investigate the inhibition of adipogenesis by natural products, Oil red O staining was performed. 3T3-L1 preadipocytes were seeded in 12-well plates until confluence, then treated with or without the natural products in the medium throughout the experiment. After 48h, the cells were differentiated, through the differentiation and maintenance steps as described above. On the tenth day after differentiation, the cells were rinsed twice with PBS, and then fixed with 4% paraformaldehyde solution for 30min. After being air dried completely, 0.5% oil-red O solution (w/v, 60% isopropanol，40% water) was added into each well and incubated for 30min at room temperature to stain. After staining, the cells were washed 3 times with distlled water and air dried for several minutes, photographed. For lipid quatification, the oil red O stained in cells was extracted with 100% isopropanol and opitical density was measured at a wavelength of 490nm (6).

2.5 Western blotting

To investigate the effects of natural products on insulin signal in insulin resistance model of 3T3-L1 adipocytes, the protein expression of insulin receptor β (IRβ), phosphor-IRβ, insulin receptor substrate-1(IRS-1), phosphor-IRS-1, Akt, phosphor- Akt and Glut-4 was measured. After 48h treated with 0.1nM human TNF-α，the adipocytes were incubated in serum-free high glucose DMEM containing 0.5% BSA, and stimulated with 100nM insulin for 3min for the study of insulin-induced tyrosine phosphorylation (5).

2.6 Glycosphingolipid analysis

Total lipids were extracted from the adipocytes, purified and separated into acidic lipid and neutral lipid fractions. Then the level of glycosphingolipid was measured with HPTLC (6).

2.7 GM3 synthase inhibition assay

To investigate whether the natural products could inhibit GM3 synthase activity, fluorescent TLC method was performed as described previously .

3. Results

3.1 Effects of the natural products on glucose uptake in insulin resistance model of 3T3-L1 adipocytes

Firstly, we examined the effects of ten compounds and four extracts on glucose uptake in 3T3-L1 adipocytes under normal and insulin resistance conditions. Fig. 1 shows that four pure compounds and three extracts enhanced glucose uptake in the insulin resistance model. As seen in Fig. 2, berberine and two extracts could enhance glucose uptake in the

normal adipocytes. Among those natural products the methanol and ethanol extracts of silkworm exerted a stronger activity than the others.

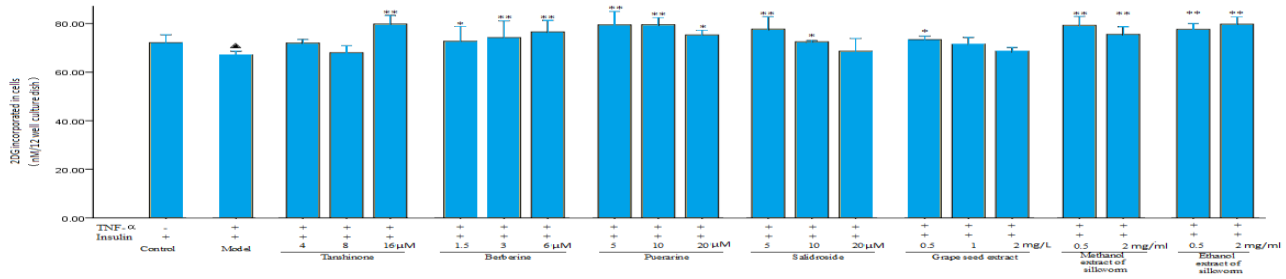


Fig.1. Four compounds and three extracts enhanced glucose uptake in the insulin resistance model of 3T3-L1 adipocytes. Data were expressed as mean ±SD (n=3).▲p＜0.05 vs Control; *p＜0.05, **p＜0.01 vs Model.

3.2 Effects of the natural products on glucose uptake in normal 3T3-L1 adipocytes

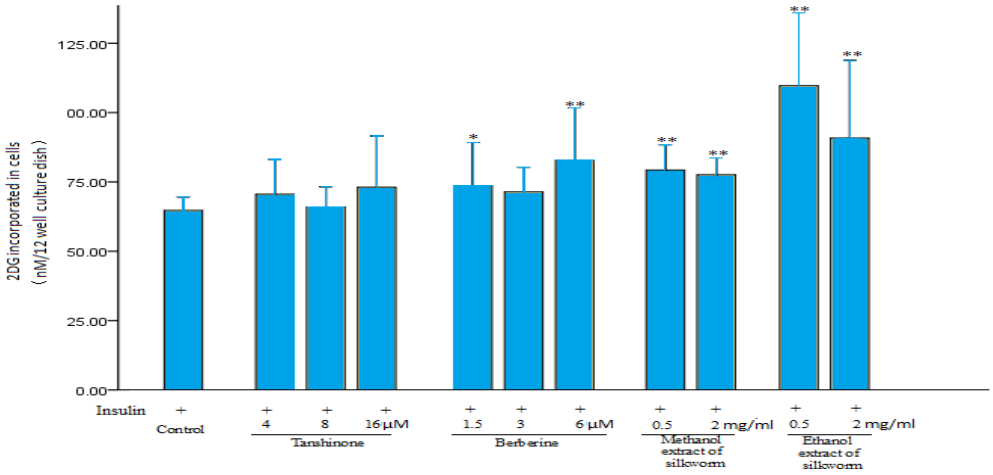
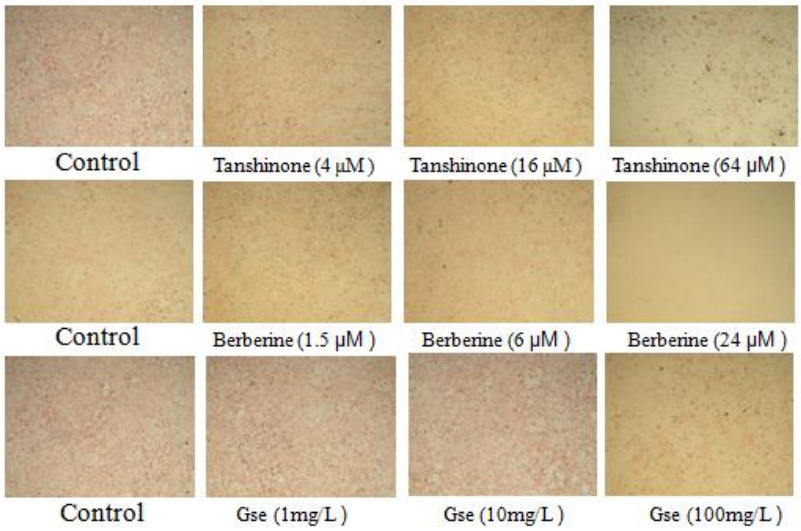


Fig.2. Berberine and two extracts enhanced glucose uptake in the normal 3T3-L1 adipocytes. Data were expressed as mean ±SD (n=3).*p＜0.05, **p＜0.01 vs Control.

3.3 Effects of the natural products on adipogenesis of 3T3-L1 preadipocytes

The anti-adipogenic activities of these natural products were evaluated by Oil red O staining and quantification methods. The results showed that tanshinone, berberine and grape seed extracts could inhibit adipogenesis significantly (Fig.3A, B).

A : microscope observation of adipocytes stained with Oil red O.



B: quantification of Oil red O.

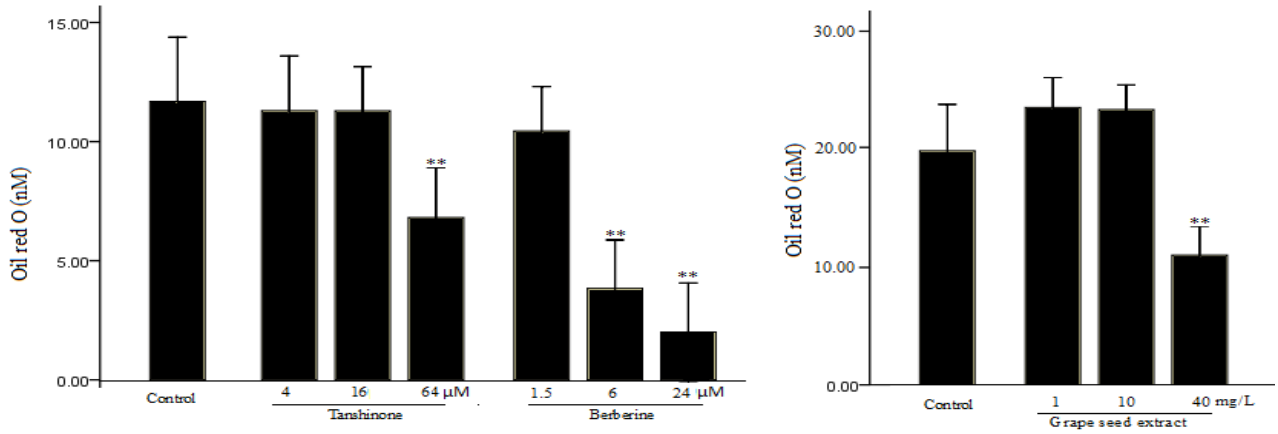


Fig.3. Inhibition of adipogenic activity by four compounds and Grape seed extract in 3T3-L1 adipocytes. (A)Photographs of Oil red O-stained lipid droplets. (B)Dissolved Oil red O absorbance was measured at 490nm. Data were expressed as the mean ±SD (n=3).*p＜0.05, **p＜0.01 vs. Control.

3.4 Effects of Tanshinone and Berberine on glycosphingolipid levels in 3T3-L1 adipocytes

We chose tanshinone and berberine which have dual activites of anti-insulin resistance and anti-adipogenesis to examine expression of glycosphingolipid GM3. As expected, tanshinone (16uM and 32uM) decreased the expression of GM3; however, berberine has no such activity.

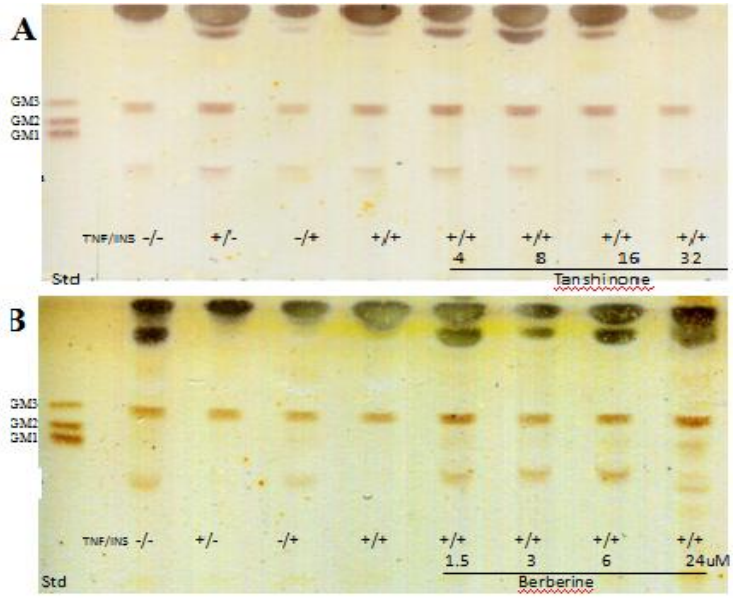


Fig.4. Effects of Tanshinone and Berberine on acidic lipid in the insulin resistance model of 3T3-L1 adipocytes

3.5 Effects of Tanshinone and Berberine on GM3 synthase activity

This results showed that both tanshinone and berberine have no inhibitory activity for GM3 synthase (Fig. 5).

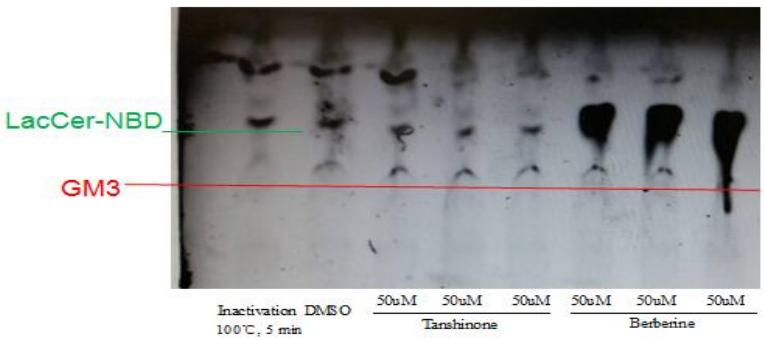


Fig.5. Effects of Tanshinone and Berberine on GM3 synthase activity in vitro.

3.6 Effects of Tanshinone and Berberine on the expression of insulin signaling related proteins

Our data showed that TNF-α decreased the level of IRS-1, berberine could reversed this state, but tanshinone has no such action. Further studies are needed to determine the mechanism underlying these effects.

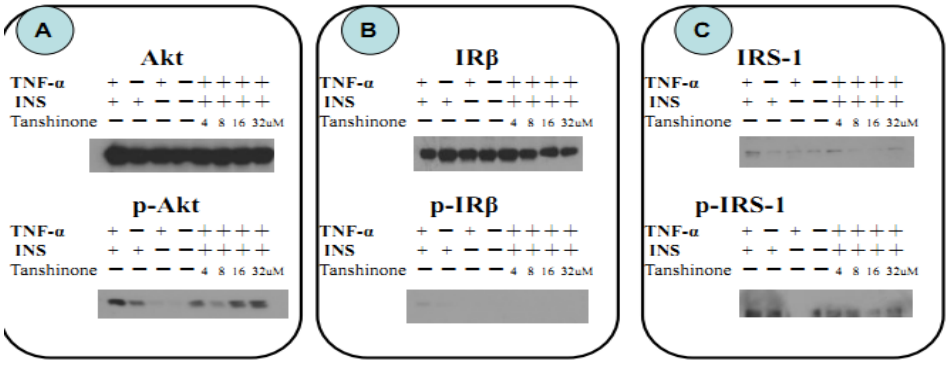


Fig.6. Effects of Tanshinone on insulin signaling related protein in the insulin resistance model of 3T3-L1 adipocytes. 3T3-L1 adipocytes were incubated in the absence or presence of 0.1nM TNF-α for 96h, meanwhile treated with different concentrations (4, 8, 16,and 32uM) of Tanshinone until the cells were collected. After 96h, the cells were stimulated with 100nM insulin(INS) for 3 min, then collected on ice. Western-blot anlysis was performed using anti-Akt and aniti –phospho-Akt(A), anti-insulin receptor β(IR β) and anti-phospho-IR β(B), anti-insulin receptor substrate-1(IRS-1) and anti phospho-IRS-1(C).

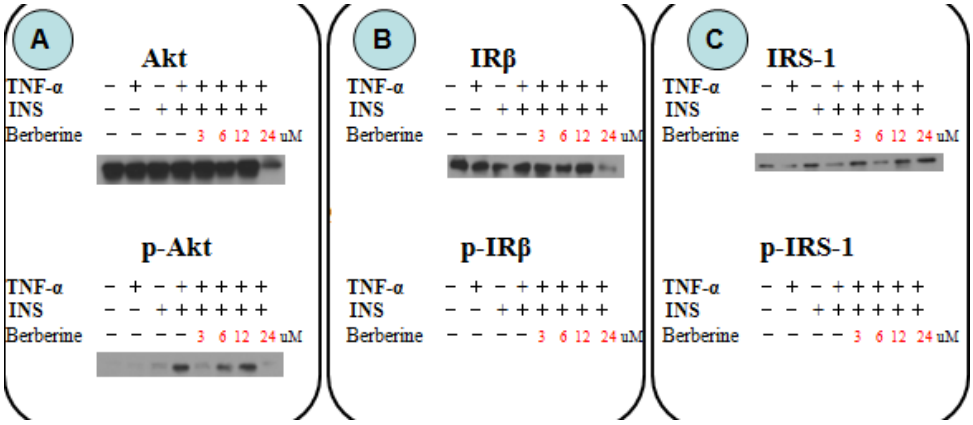


Fig.7. Effects of Berberine on insulin signaling related protein in insulin resistance model of 3T3-L1 adipocytes. 3T3-L1 adipocytes were incubated in the absence or presence of 0.1nM TNF-α for 96h, meanwhile treated with different concentrations (3, 6, 12,and 24uM) of compound Berberine until the cells were collected. After 96h, the cells were stimulated with 100nM insulin (INS) for 3 min, then collected on ice. Western-blot anlysis was performed using anti-Akt and aniti –phospho-Akt(A), anti-insulin receptor β (IR β) and anti-phospho-IR β (B), anti-insulin receptor substrate-1 (IRS-1) and anti phospho-IRS-1 (C).

4. Discussion

Our studies showed that four compounds and three extracts have beneficial effects on glucose uptake in insulin resistance model of 3T3-L1 adipocytes, and four compounds and two extracts can inhibit adipogenesis. We chose two compounds (tanshinone and berberine) to investigate the mechanisms of improving insulin resistance and reducing lipid accumulation which have both improving glucose uptake and activity of inhibiting adipogenesis. In this study, the results suggested tanshinone (32uM) can decrease the level of GM3, berberine has no such activity, wherever all the two compouns can't inhibit the activity of GM3 synthesis. The results suggested that improving insulin resistance of these two compounds is not mediated by GM3 synthesis.

In a word, this research provides a new insight on treating type 2 diabetes and obesity of natural products. According to the current results, the further investigation of the mechanism is necessary.

Acknowledgments

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作成日：2016 年 3 月 2 日

《一年間の研究業績》

■学会、研究会、報告会等での発表(在学会、研究会、报告会等的发表，请使用发表原文的语言填写)

演　　題(研究题目)	Experimental studies of astaxanthin on treating non-alcoholic fatty liver in rats		
学　会　名(学会名称)	7th Asian Community of Glycoscience and Glycotechnology (ACGG) Conference		
開　催　日(召开日期)	2015 年 11 月 12 日	開　催　地(召开地)	Sendai, Miyagi, Japan
形　　式(发表形式)	☐口演発表（口头报告）☒ポスター発表（墙报展示）		☒英語☐日本語☐中国語
共同演者名(共同演讲者)	Huang Yiqi, Luo Youhua		

演　　題(研究题目)			
学　会　名(学会名称)			
開　催　日(召开日期)	年　月　日	開　催　地(召开地)	
形　　式(发表形式)	☐口演発表（口头报告）☐ポスター発表（墙报展示）		☐英語☐日本語☐中国語
共同演者名(共同演讲者)			

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学　会　名(学会名称)			
開　催　日(召开日期)	年　月　日	開　催　地(召开地)	
形　　式(发表形式)	☐口演発表（口头报告）☐ポスター発表（墙报展示）		☐英語☐日本語☐中国語
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共同演者名(共同演讲者)			

Prognostic implication of microscopic vessel invasion and its relation with T-size categories of 8th UICC classificationin non-small cell lung cancer

非小細胞肺癌において微小脈管浸潤とUICC第８版新病期分類が術後予後に及ぼす影響の研究

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佐藤　雅昭　講師

Introduction:

We evaluated the significanceof microscopic vascular invasion (MVI)in a population of surgically managedpatients with non-small cell lung cancer (NSCLC), alongwith an analysis of the effect of the combination of MVI and tumorsize for the T-size categories according to the coming8th UICC classification of lung cancer.

Methods:

A retrospective analysis of 986 patients (pT1-4N0M0) who underwent complete surgical resectionatthe University of Tokyo Hospital, Japanbetween Jan 1979 and Oct 2010 wasconducted. LVI and BVIwereascertained using histopathological and immunohistochemicaltechniques. Survival analysis were performed based on the presence of MVI, and no MVI,age, gender, histology, and smoking status were used for multivariate analysis.

Results:

MVIwas observed in 383 of 986 patients (39%). The ratio of MVI showed a trend along with the T status, including 6 out of 121patients (5%)with T1a, 88 of 321 (27%) with T1b,106 of 247 (43%) with T1c, 76 of 137 (55%) with T2a, 54 of 77 (70%) with T2b, 40 of 60 (67%) with T3, and 12 of 23 (52%) with T4, respectively.Prevalence of MVIshowedsignificant differences in different T category ($p<0.001$, Table 1). In each T category, survival rates of patients withMVI was significantly lowerthan the corresponding MVInegativepatients.The survival rates of T1b (63.6%) and T1c(62.3%) with MVI patients were equally poor when compared to those of T2-T4without MVI patients.In a multivariate survival analysis,MVIwas an indicator of poor survival ($p<0.001$).

Conclusions:

The presenceof MVIin pN0M0 population appears to be independent poor prognosticator in surgically managed NSCLC. Those with the presence of MVImay require closer follow-up and a more aggressive treatment strategy after surgery, even if they were in the early T categories.

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths worldwide.[1] Currently, 80% of patients with lung cancer are given a diagnosis of non-small cell lung cancer (NSCLC).[2] With the improvement of technology andrecommendations to follow up the high-risk patientshave increased the probability of detecting early stage lung cancer.[3] Surgery is the most effective treatment modality for patients with early stage lung cancer, however many patients in stage I just have a 5-year survival rate ranging from 60-90%, which much lower than most other solid organ tumors.[4-7] Further, it can be seen different survival and relapse belonging to the same stage. For this reason, many studies tried to find some clinicopathologic markers that can reliably be used as prognostic indicators. Microscopic vascular invasion (MVI) is known to be a factor of poor prognosis, including intratumoral blood vessel invasion (BVI) and lymphatic vessel invasion (LVI). [8-11]Tumor categories have been redefined in the most recent 8th edition of the tumor, node, metastasis (TNM) staging system of lung cancer. Many studies have revealed the presence of MVI upstages the T stage from T1 to T2, according to the 7th TNM staging.[8-11]

Therefore, the purpose of the present study was to evaluate the impact of MVI in surgical resected patients with NSCLC in pT1-4N0M0, along with an analysis of the effect of the combination of MVI and tumor size for the T-size categories according to 8th TNM staging.

Materials and Methods

This retrospective study included surgically managed 986 patients with pathologic T1-4N0M0 at the University of Tokyo Hospital, Japan from Jan 1979 to Oct 2010. The presence of MVI was investigated on the surgical specimen, and the patients were divided into two different groups, MVI (+) and MVI (-) (MVI- : both BVI and LVI negative; MVI+ : BVI and/or LVI positive). MVI were ascertained using histopathological andimmunohistochemical techniques, and was defined as at least one tumor cell cluster visible in a lymphatic vessel or vein, respectively. None of the patients received induction chemotherapy or radiotherapy before the operation.All patients were staged according to the 8th edition of TNM staging system.

All statistical analyses were performed using SPSS 19.0 (IBM Corp, Armonk, NY). All p values were two-side. Differences were considered significant at $p<0.05$. To control for confounding variables, multivariate Cox proportional hazards regression models were used. The multivariate models initially included age, gender, histology, smoking status, and the presence or absence of MVI were used for multivariate analysis.

Results

Patients characteristics

The clinicopathologic and patient characteristics for all 986 patients are summarized in Table 1. There were 664 men

and 322 women aged 17 to 90 years (mean 65.8 years). In total, 75.1% of patients were adenocarcinoma, and 19.9% were squamous cell. 81.4% of patients underwent lobectomy, 14.8% underwent partial resection. 32% of patients were underwent by VATS (video-assisted thoracic surgery). T categories were stratified according to the newest 8th TNM edition into T1a (N=121, 12.3%), T1b (N=321, 32.6%), T1c (N=247, 25.1%), T2a (N=137, 13.9%), T2b (N=77, 7.8%), T3 (N=60, 6.1%), and T4 (N=23, 2.3%).

MVI Prevalence

Overall, MVI was observed in 383 patients (39%).The ratio of MVI showed a trend along with the T status, including 6 out of 121patients (5%)withT1a, 88 of 321 (27%) with T1b,106 of 247 (43%) with T1c, 76 of 137 (55%) with T2a, 54 of 77 (70%) with T2b, 40 of 60 (67%) with T3, and 12 of 23 (52%) with T4, respectively. Prevalence of MVI showed significant differences in different T category ($p<0.001$, Table 1). It was also significantly lower in adenocarcinoma (244 patients, 33%) than in squamous cell (106 patients, 54.1%) and the other histology (32 patients, 64%) ($p<0.001$, Table 2).

Survival Analysis

Follow-up with vital status was available for all patients. The median follow-up duration was 72 months (range, 1-120months). During the study period, a total of 313 patients died (31.7%), that is , 137 patients (43.8%) with MVI (-), 176 patients (56.2%) with MVI (+). Cancer recurrences were detected in 208 patients, that is, 87 (41.8%) with MVI (-), and 121 patients (58.2%) with MVI (+).

Figure 1a shows the overall survival(OS) curves according to the T category. The 5-year OS rates for T1a, T1b, T1c, T2a, T2b, T3, T4 groups were 88.4%, 75.4%, 70%, 56.2%, 45.5%, 48.3%, and 43.5%, respectively ($p<0.001$).Figure 1b shows the recurrence-free survival (RFS) rates for T1a, T1b, T1c, T2a, T2b, T3, T4 groups were 90.9%, 82.9%, 77.7%, 71.5%, 71.4%, 66.7%, and 73.9%, respectively ($p<0.001$).

In univariate survival analysis, the presence of MVI on the overall patient population was associated with a significant lower survival both in OS and RFS ($p<0.001$, Fig. 2).

We analyzed the study population by histology considering the three histotypes, adenocarcinoma, squamous cell carcinoma, and others. In patients with squamous cell carcinoma, the presence of MVI was associated with a poorer 5-year survival (45.3% vs. 67.8% in MVI+ and MVI-, respectively; $p=0.001$). Significantly difference also can be seen in patients with adenocarcinoma (59.0% vs. 79.8% in MVI+ and MVI-, respectively; $p<0.001$). But no significantly difference can been seen in patients with others (43.8% vs. 55.6% in MVI+ and MVI-, respectively; $p=0.681$).

Further, we analyzed the presence of MVI in each T category (Fig. 3). In T1a patients, the presence of MVI was associated with a poorer 5-year survival (83.3% vs. 88.7% in MVI+ and MVI-, respectively; $p=0.554$), maybe due to the difference in numbers (6 cases vs. 115 cases), no statistical significance had been seen. Significantly difference can

be seen in T1b (63.6% vs. 79.8%, p=0.002), T1c (62.3% vs. 75.9%, p=0.011), and T2a (47.4% vs. 67.2%, p=0.010). In T2b (38.9% vs. 60.9%, p=0.191), T3 (45.0% vs. 55.0%, p=0.588), and T4 (33.3% vs. 54.5%, p=0.268)although the presence of MVI seemed to be a lower survival, but we did not get the statistical significance. The survival rates of T1b (63.6%) and T1c (62.3%) with MVI- patients were equally poor when compared to those of T2-T4 withMVI+ patients. Figure 4 showed the RFS in each T category according to the presence of MVI.

We then performed a univariate and multivariate survival analysis using different covariates, including age, gender, T category, histology, resection, VATS, MVI, BVI, LVI, and pleural invasion (Table 3,Table4). It revealed the presence of MVI was an independent prognostic factor for OS and RFS.

DISCUSSION

The present study retrospectively evaluated the impact of MVI in the NSCLC along with the analysis of the effect of the combination of MVI and T-size categories according to the coming 8th edition of the TNM classification.

Many studies examining MVI in NSCLC demonstrated that MVI is a factor of poor prognosis for patients with NSCLC.[12-16] The previous study that used the 7th edition of the classification proposed the MVI affects both OS and RFS, which should upstage the T categories.[5,11,17] The results of our study indicate that MVI correlates with the tumor size and the histology type. MVI is an independent negative prognostic factor. The new 8th edition of the TNM classification system underestimates the presence of MVI, which has a greater prognostic impact than size.

MVI is one of the step leading to metastatic diffusion. The first studies about the prognostic role of MVI in lung cancer date back to the late 1950s. Since then, numerous studied have investigated the importance of MVI in the progression of lung cancer.Aokage et al.[18] analyzed resected NSCLC with pulmonary metastases and revealed that some pulmonary metastases may be the result of lymphatic tumor spread. They hypothesized that tumor cells in the lymphatic vessels in bronchovascular bundles transmigrate to the lung parenchyma and develop intrapulmonay metastases. Dvorak et al.[19] suggested that a high rate of neovascularization could facilitate cancer cells easy invasion into blood vessels and thereby facilitate the metastatic process, meanwhile the newly formed blood vessels were of a leaky nature, increasing their permeability and making the vascular invasion easier to accomplish.Despite growing evidence revealedMVI play a crucial role for the prognosis in NSCLC, but no TNM classification system of lung cancer so far has incorporated MVI in the determinants of prognosis, and even the coming 8th edition of the TNM staging. Because our study was a retrospective study in a single institution, we need to collect more clinicopathological date from a diverse population, further prospective, large-size studies are required to confirm our results.

CONCLUSION

We conclude that the presence of MVI in resected patients with pT1-4N0M0 NSCLC in the surgical specimen is frequent. It appears to be independent poor prognosticator in surgically managed NSCLC, which in our experience was a more important prognostic determinant than size according to the coming 8th TNM staging system. Patients with MVI are therefore to be considered a high-risk group among patients with early-stage NSCLC, who may be required closer follow-up and a more aggressive treatment strategy after surgery.

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Table 2. MVI prevalence

	N (%)	MVI [n (%)]		p value
		-	+	
All case	**986**	**604 (61.3)**	**382 (38.7)**	
Age, mean (range)	65.8 (17-90)			**0.856**
⩽70 years	616 (62.5)	376 (61.0)	240 (39.0)	
> 70 years	370 (37.5)	228 (61.6)	142 (38.4)	
Gender				**<0.001**
Male	664 (67.3)	359 (54.1)	305 (45.9)	
Female	322 (32.7)	245 (76.1)	77 (23.9)	
Histology				**<0.001**
Adenocarcinoma	740 (75.1)	496 (67.0)	244 (33.0)	
Squamous cell	196 (19.9)	90 (45.9)	106 (54.1)	
Others	50 (5.1)	18 (36)	32 (64)	
VATS				**<0.001**
Yes	316 (32)	249 (78.8)	67 (21.2)	
No	670 (68)	355 (53.0)	315 (47.0)	
Resection				**<0.001**
Lobectomy	803 (81.4)	465 (57.9)	338 (42.1)	
Segmentectomy	34 (3.4)	26 (76.5)	8 (23.5)	
Partial resection	146 (14.8)	112 (76.7)	34 (23.3)	
Pneumonectomy	3 (0.3)	1 (33.3)	2 (66.7)	
T size, mm, mean (range)	27.6 (4-150)			
T categories*				**<0.001**
T1a (⩽10mm)	121 (12.3)	115 (95)	6 (5)	
T1b (⩽20mm)	321 (32.6)	233 (72.6)	88 (27.4)	
T1c (⩽30mm)	247 (25.1)	141 (57.1)	106 (42.9)	
T2a (⩽40mm)	137 (13.9)	61 (44.5)	76 (55.5)	
T2b (⩽50mm)	77 (7.8)	23 (29.9)	54 (70.1)	
T3 (⩽70mm)	60 (6.1)	20 (33.3)	40 (66.7)	
T4 (>70mm)	23 (2.3)	11 (47..8)	12 (52.2)	
Pleural invasion				**<0.001**
Absent	654 (66.3)	490 (74.9)	164 (25.1)	
Present	332 (33.7)	114 (34.3)	218 (65.7)	
Recurrence				**<0.001**
Absent	778 (78.9)	517 (66.5)	261(33.5)	
Present	208 (21.1)	87 (41.8)	121 (58.2)	

* According to the 8th TNM staging system

Table 3 Overall survival

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
MVI	2.407 (1.924-3.010)	<0.001	1.884 (1.442-2.781)	<0.001
BVI	1.719 (1.528-1.934)	<0.001	--	--
LVI	1.687 (1.355-2.100)	<0.001	--	--
Gender	2.442 (1.832-3.254)	<0.001	1.895 (1.411-2.545)	<0.001
Age	2.061 (1.647-2.578)	<0.001	2.155 (1.710-2.716)	<0.001
Histology	1.391 (1.237-1.565)	<0.001	1.204 (1.054-1.376)	0.006
VATS	0.770 (0.596-0.995)	0.046	--	--
Resection	1.029 (0.885-1.195)	0.711	--	--
8th pT categories	1.348 (1.260-1.442)	<0.001	1.208 (1.114-1.310)	<0.001
Pleural invasion	2.305 (1.846-2.878)	<0.001	1.507 (1.172-1.939)	0.001

The multivariate Cox regression models initially included MVI status, BVI, LVI, gender, age, histology, VATS, resection, 8th pT categories, pleural invasion. A backward elimination was performed with a threshold of p=0.05.

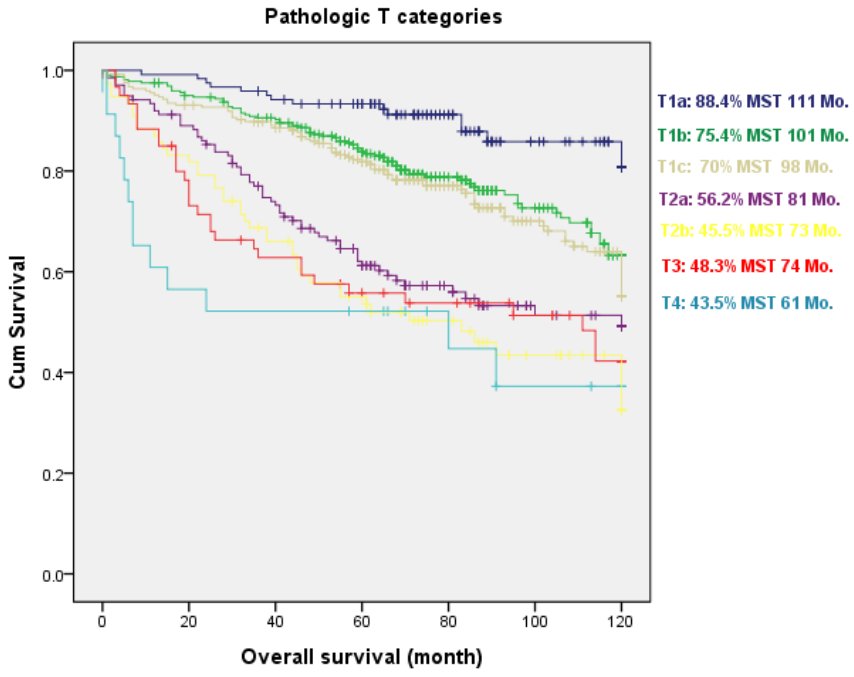
CI: confidence interval, HR: hazard ratio, OS: overall survival

MVI: microscopic vascular invasion, BVI: blood vessel invasion, LVI: lymphatic vessel invasion

VATS: video-assisted thoracoscopic surgery

Figure 1 Overall survival and recurrence-free survival of the study population according to the T-size categories of 8th TNM staging. MST, mean survival time.

a.



b.

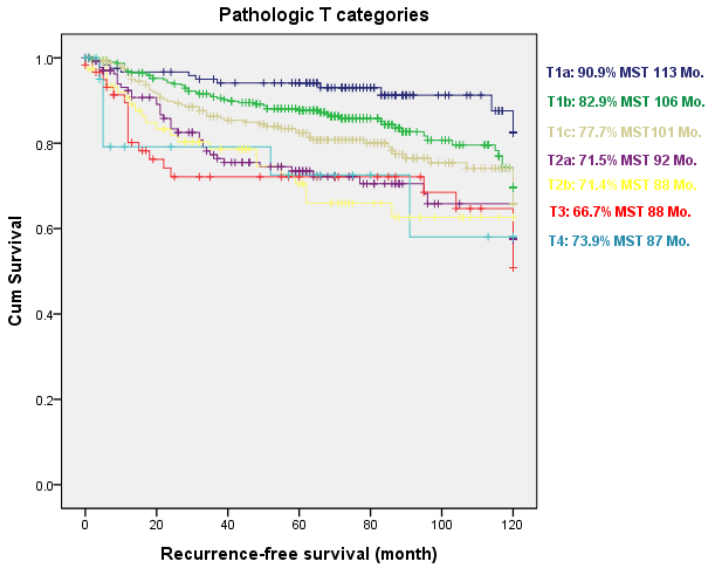
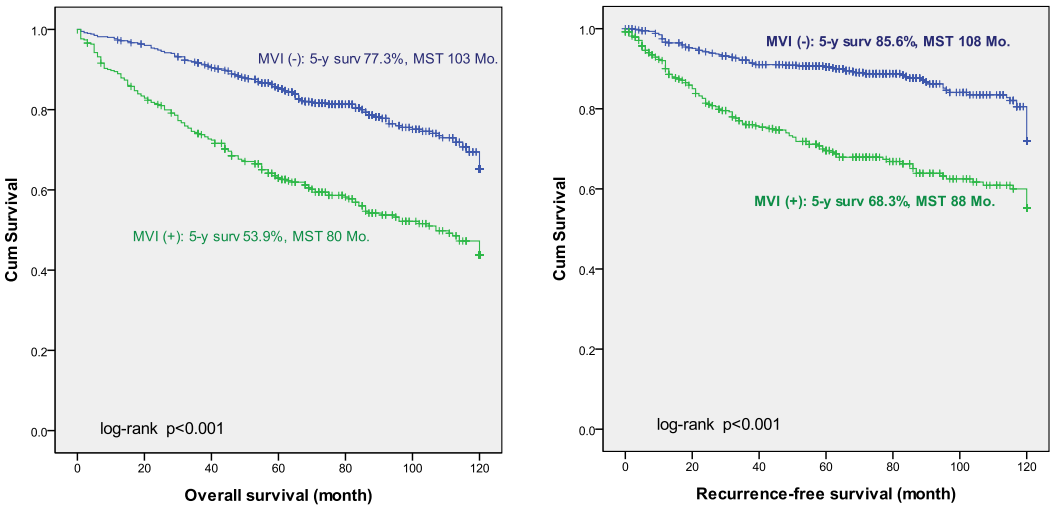


Figure 2 Overall survival and recurrence-free survival of the study population according to the presence/absence of microscopic vascular invasion. MST, mean survival time.



作成日：2016年2月29日

《一年間の研究業績》

■学会、研究会、報告会等での発表(在学会、研究会、报告会等的发表，请使用发表**原文的语言**填写)

演　　題(研究題目)	Tumor-associated CD204+ macrophages is a prognostic marker in clinical stage I lung adenocarcinoma		
学　会　名(学会名称)	The 24th Annual Meeting of Asian Society for Cardiovascular and Thoracic Surgery(ASCVTS)		
開　催　日(召开日期)	2016 年 4 月 6 日	開　催　地(召 开 地)	Taibei
形　　式(发表形式)	☒口演発表（口头报告）☐ポスター発表（墙报展示）		☒英語☐日本語☐中国語
共同演者名(共同演讲者)			

演　　題(研究題目)	Prognostic implication of microscopic vessel invasion and its relation with T-size categories of 8th UICC classification in non-small cell lung cancer		
学　会　名(学会名称)	24th European Conference on General Thoracic Surgery		
開　催　日(召开日期)	2016 年 5 月 29 日	開　催　地(召 开 地)	Naples,Italy
形　　式(发表形式)	☒口演発表（口头报告）☐ポスター発表（墙报展示）		☒英語☐日本語☐中国語
共同演者名(共同演讲者)			

演　　題(研究題目)			
学　会　名(学会名称)			
開　催　日(召开日期)	年　月　日	開　催　地(召 开 地)	
形　　式(发表形式)	☐口演発表（口头报告）☐ポスター発表（墙报展示）		☐英語☐日本語☐中国語
共同演者名(共同演讲者)			

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学　会　名(学会名称)			
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形　　式(发表形式)	☐口演発表（口头报告）☐ポスター発表（墙报展示）		☐英語☐日本語☐中国語
共同演者名(共同演讲者)			

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