国立病院機構鹿児島医療センター

研究業績集　第22号

令和3年4月～令和4年3月(2021 年 4 月～2022 年 3 月)

国立病院機構鹿児島医療センター

臨床研究部

はじめに

鹿児島医療センター研究業績集第 22 号の発刊にあたって

令和 3 年度（2021 年度）研究業績集第 22 号を発刊する運びとなりました。平成 11 年（1999 年）に始まり、22 冊目となります。今回の論文数は総説を含めて 40 編（英文 23 編、和文 17 編）、学会報告 96 件（国際 4 件、国内 92 件）でした。残念ながら原著論文の大幅な減少を認めます。コロナ禍の影響はあるかもしれませんが、研究に対する活性化を図る必要性があると感じています。次年度を期待したいと思います。

新型コロナ感染症の流行が始まり、丸3年経過しました。様々な活動が制限され、また、感染管理に時間を費やさざるを得ない状況が続いています。いまだに強い感染力を有していますが、弱毒化は確実に進み、収束しつつあるのではないでしょうか。以前のコロナウイルスの定位置に収まり、風邪症候群の一つになることを期待しています。ただ、このコロナの影響は研究部門にも大きな影を落としています。当院の研究活動も巻き込まれてしまいましたが、全国的にその傾向はあるかもしれません。ただ、その中でも持続できている施設もあります。どのような状況でもぐらつかない強靭なシステムを構築していると思われます。

今の日本全体の研究意欲、特に医学に関しては低下していると感じます。ノーベル賞クラスの研究は過去の実績で、各個人のとてつもない努力で成しえてきたと思います。今からの研究は当事者の頑張りはもちろんですが、透明性の担保や莫大な情報 Data に対応するため、システムが重要と思います。今まで世界をけん引してきた日本の研究分野も組織疲労がでており、再構築する必要性を感じています。

現在活躍している中堅クラスの研究家も、もう一度研究の面白さや、知的欲求の重要性などを若い医師や学生に伝達し、日本の研究が持続可能なものになることを期待しています。当センターでも研究や研修ができる病院を目指しています。もう一度原点に戻り、研究意欲を高めたいものです。

令和 4 年 12 月

独立行政法人国立病院機構鹿児島医療センター

田 中 康 博

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1. 臨床研究部の組織概要

1. 名称・所在地

独立行政法人国立病院機構鹿児島医療センター臨床研究部

鹿児島県鹿児島市城山町８－１

2. 沿革

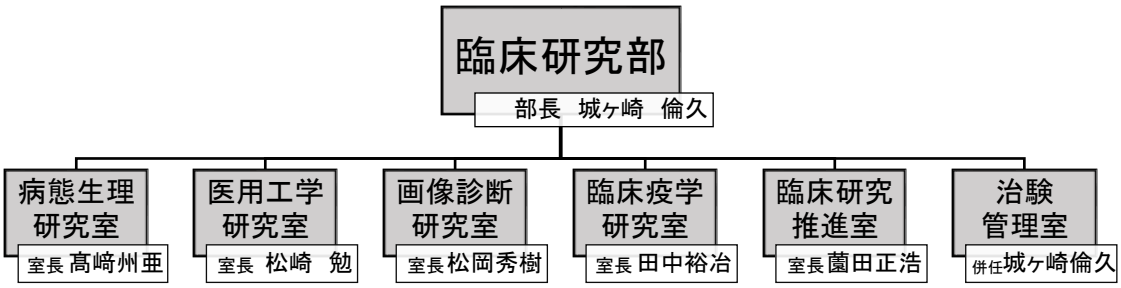
臨床研究部は 1999 年 10 月に設置されました。当初は病態生理研究室、医用工学研究室、画像診断研究室、臨床疫学研究室、治療評価研究室の 5 室で運営されていましたが、2007 年に治療評価研究室を臨床研究推進室と名称変更を行い、さらに 2013 年からは治験管理室を加え、現在 1 部 6 室で活動しています。2006 年からは東病棟 8 階に臨床研究部・治験管理室がありましたが、2018 年 4 月の逓信病院機能移転に伴い、2017 年 11 月に臨床研究部は旧更衣棟に、治験管理室は事務棟に移転しました。

3. 組織構成

臨床研究部長の総括のもとに以下の研究室を設置しています。

1. 病態生理研究室
2. 医用工学研究室
3. 画像診断研究室
4. 臨床疫学研究室
5. 臨床研究推進室
6. 治験管理室

令和2年度の臨床研究部の各室の体制は以下に示す通りです。



4. 鹿児島大学大学院医歯学総合研究科

当院は平成 21 年より、鹿児島大学の連携大学院となっており、先進医療学講座（連携講座）生理活性物質制御学を開講しています。

これまでに 5 人の学生が臨床研究部で研究を行い、鹿児島大学大学院医歯学総合研究科の大学院博士号を取得しました。

5. 臨床研究部の活動

1）臨床研究

NHO 共同研究として自己免疫性疾患特異的 iPS 細胞を国立病院機構弘前病院に提供し、共同研究を行っています。

本部主導大規模臨床研究（EBM 研究）としては 5 件の課題に参加しています。内訳としては外科 2 件、血液内科 1 件、糖尿病・内分泌内科 1 件、循環器内科 1 件でした。

NHO ネットワーク研究にも積極的に参加しており 12 件の課題があります。内訳としては血液内科が 4 件、臨床研究部主導、病理診断科、糖尿病・内分泌内科が各 2 件、脳血管内科、外科が各 1 件、でした。

NHO が主導する研究以外でも、各診療科、コメディカル、看護部、看護学校で独自の研究が行われており、研究課題数は全部で 90 課題ありました。

2）競争的研究費

歯科口腔外科の中村康典先生が日本学術振興会科学研究費補助金の基盤研究（C）を主任研究者として 1 件獲得されました。また、基盤研究（C）については歯科口腔外科と腫瘍内科が分担研究者として各 1 件獲得しています。

厚生労働省科学研究費を小児科が 2 件、日本医療開発研究機構研究費を皮膚腫瘍科・皮膚科が 3 件をいずれも分担研究者として獲得しています。

民間セクターからの寄付金は 9 件あり、心臓血管外科、消化器内科、外科、放射線室が各 2 件、皮膚腫瘍科・皮膚科が 1 件でした。

3）治験・製造販売後調査

2021 年度（令和 3 年度）は新規治験が 1 件ありました。継続契約の治験は第Ⅱ相が 2 件、第Ⅲ相が 3 件でした。そのうち医薬品の治験が 5 件、再生医療の治験が 1 件ありました。診療科の内訳としては血液内科が 3 件、脳血管内科が 2 件、婦人科が 1 件でした。

2021 年度に終了した治験としては契約件数が 4 件であり、契約症例 10 件のうち実施症例が 10 件であり実施率としては 100%でした。

NHO 指定臨床研究として参加した「新型コロナワクチンの投与開始初期の重点的調査（コホート調査）」は令和 4 年 3 月に終了しましたが、その後 PMS 研究(コミナティ筋注一般使用成績調査)として 222 名を追跡調査中です。それ以外の製造販売後調査については、今年度新規登録のあった課題が 24 件ありました。内訳としては血液内科が 9 件、循環器内科が 7 件、皮膚腫瘍科・皮膚科が 4 件、糖尿病・内分泌内科、消化器内科、小児科、腫瘍内科が各々1 件でした。

2021 年度の受託研究請求額は 1,331 万円でした。

4）倫理審査委員会・治験審査委員会・研究倫理教育の推進

倫理審査委員会および治験審査委員会は 2021 年度に各々8 回開催しました。両審査委員会の外部委員として、元南日本新聞の有川賢司先生と元小学校校長の江口惠子先生に引き続きご協力いただいています。

臨床研究を行う上で倫理教育が必須です。国立病院機構では臨床研究に関わる全ての職員

に研究倫理教育 e ラーニングプログラムである eAPRIN の受講を行っています。臨床研究部では鹿児島医療センターの eAPRIN の受講登録・管理・受講支援を行っています。今年度は 380 名が受講修了しました。

5）学会発表・論文発表 （当院所属として機構本部が認めたもの）

学会発表については、国内学会が 92 題、国際学会が 4 題でした。論文については、英語論文は 23 編、そのうち当院職員が筆頭者になっている英文原著論文は 2 編でした。和文原著・総説は 17 編、そのうち当院職員が筆頭者になっているものは 13 編でした。

＜業績発表、独自研究＞

WoS／PubMED 掲載英文論文		
英文原著論文（筆頭筆者以外）	15	本
英文原著論文（筆頭筆者）	2	本
英文原著論文以外（筆頭筆者以外）	3	本
英文原著論文以外（筆頭筆者）	3	本
和文原著論文等（筆頭筆者）	13	本
和文原著論文等（筆頭筆者以外）	4	本
国際学会発表（演者のみ）	4	回
国内学会発表（演者のみ） ＊総会、地方会、シンポジウム、一般演題含む	92	回

6）日本学術振興会科学研究費申請

日本学術振興会科学研究費の申請にあたって「研究機関における公的研究費の管理・監査のガイドライン（実施基準）」に基づく「体制整備等自己評価チェックリスト」および、「研究活動における不正行為への対応等に関するガイドラインに基づく取組状況に係るチェックリスト」を提出する必要があります。臨床研究部では、毎年この 2 つのチェックリストを文部科学省に提出しています。また「体制整備等自己評価チェックリスト」については厚生労働省にも提出しています。

研究費の不正使用防止に向けた取り組みとして、公的研究費を使用されているすべての医師、事務職員、管理者に対してコンプライアンス教育のための動画を作成し、視聴後に誓約書を提出していただいています。

7）鹿児島市医報学術への寄稿

当院は毎年 2 回春と秋に鹿児島市医報の「学術」コーナーに寄稿しています。

今年度は第 60 巻 9 号に外科の菰方先生の「肝門部胆管内発育を伴った cStageIVc 大腸癌に対する手術と薬物のタッグ療法」が、第 61 巻 3 号には心臓血管外科の永冨先生の「血行動態破綻をきたしたアルカプトン尿症に合併する大動脈弁狭窄症の一例」が掲載されました。

2. 臨床研究と治験

① 臨床研究

（ア）NHO 指定臨床研究

種別	研究責任医師	研究課題名
厚生労働科学研究 （指定研究）20HA2013	城ヶ崎倫久	新型コロナワクチンの投与開始初期の重点的調査（コホート調査）
NHO 共同研究	城ヶ崎倫久	自己炎症性疾患特異的 iPSC 細胞の培養ストックの作成及び分化誘導

（イ）EBM 研究

領域・課題番号	研究責任医師	研究課題名
特定臨床研究 H26-EBM(介入)-03	菰方輝夫	膵がん切除後の補助化学療法における S-1 単独療法と S-1 とメトホルミンの併用療法の非盲検ランダム化第Ⅱ相比較試験（ASMET 研究）
H26-遺伝子-02	大塚眞紀	未治療多発性骨髄腫における遺伝子解析による治療感受性・予後予測因子の探索的研究(NGSMM 研究)
H26-遺伝子-03	郡山暢之	日本人の肥満症の発症と治療効果・抵抗性に関連する遺伝素因の探索 -オーダーメイド医療の確立-（G-FORCE 研究）
特定臨床研究 H27-EBM(介入)-01	菰方輝夫	免疫抑制患者に対する 13 価蛋白結合型肺炎球菌ワクチンと 23 価莢膜多糖体型肺炎球菌ワクチンの連続摂取と 23 価莢膜多糖体型肺炎球菌ワクチン単独摂取の有効性の比較 -二重盲検無作為化比較試験-（CPI Study）
H29-EBM(観察)-02	中島 均	我が国における左冠動脈主幹部インターベンションに対するコホート研究(LM-JANHO)

（ウ）NHO ネットワーク共同研究

領域	研究責任医師	研究課題名
H27-NHO(糖尿)-01	郡山暢之	多面的管理達成者の糖尿病腎症予後改善効果を予測できる非侵襲的指標の確立（DNrem研究）
H29-NHO(脳卒中)-01	松岡秀樹	虚血性脳卒中患者における脳微小出血進展への抗血栓薬の関与に関する研究
H28-NHO（血液）-02	大塚眞紀	成人初発未治療びまん性大細胞型 B 細胞リンパ腫における R CHOP 単独治療と放射線併用療法の治療成績、 QOL 、費用、費用対効果の多施設共同前向きコホート研究
H28-NHO(多共)-02	野元三治	メトトレキサート(MTX)関連リンパ増殖性疾患の病態解明のための多施設共同研究
H30-NHO(糖尿病)-01	郡山暢之	多面的管理達成者の糖尿病性腎臓病（DKD)予後改善効果評価法の確立と、効果予測のための非侵襲的指標の確立（DKDrem-2 研究）
H30-NHO(循環)-01	城ヶ崎倫久	真の心房細動発症リスク同定のための新規バイオマーカー CA-125 の検討（CA125-AF）

領域	研究責任医師	研究課題名
H31-NHO(血液)-01	大塚眞紀	未治療濾胞性リンパ腫における Obinutuzumab の治療成績、QOL、費用対効果、予後に関する多施設前向きコホート研究（PEACE-FL）
H31-NHO(血液)-02	大塚眞紀	B 細胞性急性リンパ性白血病におけるターゲットキャプチャー RNA-seq を用いたサブタイプ診断の実行可能性に関する研究
H31-NHO(多共)-02	野元三治	メトトレキサート(MTX)関連リンパ増殖性疾患の遺伝子変異プロファイルの解析
R2－NHO(心脳)-04	城ヶ崎倫久	がん化学療法関連心筋症の予測、早期発見、早期治療 ～心臓超音波検査 speckle tracking 法、タイチン truncating 変異の検出、尿中タイチン N フラグメント測定、血中心筋トロポニン I 高感度測定の比較検討～
R3－NHO(血液)-01	大塚眞紀	レジストリ―データを利用した AYA 世代 DLBCL の臨床的・生物学的特性を明らかにする観察研究（NHO-DLBCL-AYA 研究）
R3-NHO(消化)-01	菰方 輝夫	膵癌における腹腔洗浄細胞診を補完する新規バイオマーカーの確立に関する研究

(エ) 競争的研究費等

I. 公費臨床試験

財源	課題名	研究者名	金額(円)
厚生労働省 厚生労働科学研究費補助金	小児から成人期発症遺伝性 QT 延長症候群の突然死予防に関する研究	分担研究者 吉永正夫	100,000
厚生労働省 厚生労働科学研究費補助金	特発性心筋症に関する調査研究	分担研究者 吉永正夫	300,000
日本医療研究開発機構研究費	進行性悪性黒色腫治療における抗 PD-1 抗体との TM5614 の安全性・有効性を検討する第Ⅱ相試験	分担研究者 松下茂人	260,000
文部科学省 科学研究費助成事業 基盤研究(C)	摂食機能評価に基づいた栄養食事指導の有効性と体組成改善への影響の検討	分担研究者 中村康典	50,000
文部科学省 科学研究費助成事業 基盤研究(C)	心臓弁膜症術後合併症制御に対する医学管理における系統的口腔管理の構築	主任研究者 中村康典	1,100,000
文部科学省 科学研究費助成事業 基盤研究(C)	心臓弁膜症術後合併症制御に対する医学管理における系統的口腔管理の構築	分担研究者 城ヶ崎 倫久	52,000
文部科学省 科学研究費助成事業 基盤研究(C)	心臓弁膜症術後合併症制御に対する医学管理における系統的口腔管理の構築	分担研究者 金城玉洋	52,000
文部科学省 科学研究費助成事業 基盤研究(C)	心臓弁膜症術後合併症制御に対する医学管理における系統的口腔管理の構築	分担研究者 片岡哲郎	52,000
文部科学省 科学研究費助成事業 基盤研究(C)	心臓弁膜症術後合併症制御に対する医学管理における系統的口腔管理の構築	分担研究者 平峯聖久	52,000

財源	課題名	研究者名	金額（円）
文部科学省 科学研究費助成事業　基盤研究（C）	心臓弁膜症術後合併症制御に対する医学管理における系統的口腔管理の構築	分担研究者 本庄希恵	39,000
文部科学省 科学研究費助成事業　基盤研究（C）	心臓弁膜症術後合併症制御に対する医学管理における系統的口腔管理の構築	分担研究者 下田平佳純	26,000
日本医療研究開発機構研究費	頭頸部基底細胞癌縮小マージン切除による新たな低侵襲標準治療の開発	分担研究者 松下茂人	1,170,000
日本医療研究開発機構研究費	爪部悪性黒色腫への指趾骨温存切除による新たな低侵襲標準治療の開発	分担研究者 松下茂人	260,000
科学研究費助成事業　基盤研究（C）	生体内ゲノム編集を利用したHTLV-1を標的にする新規抗ウイルス療法	分担研究者 魚住公治	130,000

II. 民間セクターからの寄付金

課題名/依頼業者名	研究者名	金額（円）
高齢者の血管疾患に対する外科治療の研究/日本ライフライン株式会社	金城　玉洋	600,000
肝細胞がんに対する肝動脈塞栓療法に関する研究/株式会社ユー・ティー・エム	櫻井　一宏	100,000
急性皮膚潰瘍での創収縮のダイナミック解析と筋繊維芽細胞の形態構築動態解析の研究助成/科研製薬株式会社	松下　茂人	200,000
安全な消化器外科手術に対する研究/科研製薬株式会社	菰方　輝夫	150,000
核医学画像診断技術の研究（核医学的手法を用いた画像診断に関する研究）/富士フィルム富山化学株式会社	杉尾　浩	500,000
心臓核医学に関する研究/日本メジフィジックス株式会社	杉尾　浩	500,000
肝細胞がんに対する肝動脈塞栓療法に関する研究/株式会社ユー・ティー・エム	櫻井　一宏	100,000
外科手術の安全性に関する臨床研究/KMバイオロジクス株式会社	菰方　輝夫	100,000
心臓血管外科手術手技の研究/KMバイオロジクス株式会社	金城　玉洋	100,000

（オ） 臨床研究課題

	研究内容・課題名	部署・研究者名
1	非弁膜症性心房細動を有する後期高齢患者を対象とした前向き観察研究（ANAFIE Registry）	第1循環器内科 片岡哲郎
2	深部静脈血栓症及び肺血栓塞栓症の治療及び再発抑制に対するリバーロキサバンの有効性及び安全性に関する登録観察研究（J'xactly Study）	第1循環器内科 中島　均
3	大動脈瘤/大動脈解離患者の実態調査および予後に関する前向き観察研究	第1循環器内科 中島　均
4	動脈硬化を基盤とした虚血性心臓病における新規血液マーカーの確立	第1循環器内科 中島　均

	研究内容・課題名	部署・研究者名
5	2 管球 CT を用いた冠動脈狭窄、心筋虚血、心筋線維化の総合的評価に関する多施設研究（AMPLIFiED）	第 1 循環器内科 中島　均
6	エベロリムス溶出性コバルトクロムステント（CoCr-EES[XIENCE]）留置後の DAPT 投与期間を 1 か月に短縮することの安全性を評価する多施設前向きオープンラベル無作為化比較試験（ShorT and Optimal duration of Dual AntiPlatelet Therapy study-2(STOPDAPT-2)	第 1 循環器内科 中島　均
7	高尿酸血症に対するキサンチンオキシダーゼ阻害剤フェブキソスタットの血管障害予防効果に関する多施設共同ランダム化比較試験（PRIZE study）	第 1 循環器内科 中島　均
8	SGLT2 阻害薬による動脈硬化予防の多施設共同ランダム化比較試験（PROTECT）	第 1 循環器内科 中島　均
9	実地臨床におけるバイオリムス溶出性ステント（BES）とエベロリムス溶出性ステント（EES）の有効性及び安全性についての多施設前向き無作為化オープンラベル比較試験（NEXT）	第 1 循環器内科 中島　均
10	至適な血管内超音波ガイド経皮的冠動脈インターベンションの複雑性病変における臨床経過を評価する前向き観察研究（OPTIVUS）	第 1 循環器内科 中島　均
11	破裂性腹部大動脈瘤に対する開腹手術とステントグラフト内装術の治療選択に関する全国多施設観察研究	心臓血管外科 川津祥和
12	非弁膜症性心房細動とアテローム血栓症を合併する脳梗塞例の二次予防における最適な抗血栓療法に関する多施設共同ランダム化比較試験（Optimal Antithrombotic Therapy in Ischemic Stroke Patients with Non-Valvular Atrial Fibrillation and Atherothrombosis：ATIS-NVAF）	脳血管内科 松岡秀樹
13	脳卒中研究者新ネットワークを活用した脳・心血管疾患における抗血栓療法の実態と安全性の解明（The Bleeding with Antithrombotic Therapy Study 2：BAT2）	脳血管内科 松岡秀樹
14	虚血性脳卒中患者における脳微小出血進展への抗血栓薬関与に関する研究	脳血管内科 松岡秀樹
15	K-RESOLVE Network 研究	脳血管内科 松岡秀樹
16	機械的血栓回収療法による再開通後の脳循環時間と再潅流障害との関連についての研究	脳血管内科 濵田祐樹
17	新型コロナウイルス感染症（COVID-19）に脳卒中を発症した患者の臨床的特徴を明らかにする研究 -今後拡大が予測される COVID-19 への対策の模索-	脳血管内科 松岡秀樹
18	レセプト等情報を用いた脳卒中・脳神経外科医療疫学調査（J-ASPECT study : Nationwide survey of Acute Stroke care capacity for Proper dEsignation of Comprehensive stroke CenTer in Japan）	脳血管内科 松岡秀樹
18	血管モデルを用いた有効な血栓回収療法手技の確立に関する研究	脳血管内科 濵田祐樹
19	くも膜下出血アウトカム評価ツールの日本語版開発（SAHOT-J）	脳神経外科 久保文克
20	脳卒中患者の長期予後追跡のための QOL データ収集システムの開発（PROP-J）	脳神経外科 久保文克
21	Double-Layer Carotid Stent の治療	脳神経外科 久保文克
22	未破裂脳動脈瘤に対する脳血管内治療	脳神経外科 久保文克
23	小児から成人期発症遺伝性 QT 延長症候群の突然死予防に関する研究	小児科 吉永正夫

	研究内容・課題名	部署・研究者名
24	特発性心筋症に関する調査研究	小児科 吉永正夫
25	高齢者移植非適応再発・難治末梢性 T 細胞リンパ腫に対するゲムシタビン、デキサメサゾン、シスプラチン（GDP）療法＋ロミデプシン療法の第 II 相試験	血液内科 大塚眞紀
26	未治療 CCR4 陽性高齢者 ATL に対するモガムリズマブ併用 CHOP-14 の第 II 相試験	血液内科 大塚眞紀
27	骨髄増殖性腫瘍の実態と遺伝子変異検索	血液内科 大塚眞紀
28	未治療濾胞性リンパ腫における Obinutuzumab の治療成績、QOL、費用対効果、予後に関する多施設前向きコホート研究	血液内科 大塚眞紀
29	B 細胞性急性リンパ性白血病におけるターゲットキャプチャーRNA-seq を用いたサブタイプ診断の実行可能性に関する研究	血液内科 大塚眞紀
30	成人 T 細胞白血病リンパ腫における CCR4 遺伝子変異と予後の検討	血液内科 大塚眞紀
31	血小板減少を呈する患者における酵素測定法によるゴーシェ病スクリーニング	血液内科 大塚眞紀
32	切除不能肝細胞癌に対するレンバチニブ早期投与効果についての多施設共同研究	消化器内科 櫻井一宏
33	免疫抑制患者を対象とした PCV13/PPSV23 と PPSV23 の予防効果の比較試験	外科 菰方輝夫
34	膵癌における腹腔洗浄細胞診を補完する新規バイオマーカーの確立に関する研究	外科 菰方輝夫
35	アバスチン点滴静注用　特定使用成績調査「進行又は再発の子宮頸癌」	婦人科
36	ヘパリン Na 注 1 万単位/10mL「モチダ」 副作用調査 「ヘパリンナトリウムの投与によって発現した腹腔内出血に対する副作用調査」	婦人科
37	GOTIC-002　局所進行子宮頸癌根治放射線療法施行例に対する UFT による補助化学療法のランダム化第Ⅲ相比較試験	婦人科
38	PFAPA 症候群における口蓋扁桃摘出術の効果検討	耳鼻咽喉科 伊東小都子
39	副甲状腺腫瘍術後における低カルシウム血症の検討	耳鼻咽喉科 西元謙吾
40	Experience of radiotherapy during the nosocomial cluster of coronavirus disease-19 in a regional core hospital	放射線科 上山友子
41	放射線治療の治療効果評価法・合併症低減法	放射線科
42	オクトレオスキャン症例の解析	放射線科
43	骨転移のある前立腺癌に対する塩化ラジウム治療	放射線科
44	塩化ラジウム治療における MRI の評価	放射線科
45	メトトレキサート(MTX)関連リンパ増殖性疾患の遺伝子変異プロファイルの解析	病理診断科 野元三治

	研究内容・課題名	部署・研究者名
46	ブルーリ潰瘍（M.ulcerans 感染症）における無痛性病態メカニズムの解明	病理診断科 後藤正道
47	呼吸上皮腺腫様過誤腫の病理学的特徴と疫学に関する研究	病理診断科 後藤正道
48	心臓弁膜症術後合併症制御に対する医学管理における系統的口腔管理の構築	歯科口腔外科 中村康典
49	骨吸収抑制薬関連顎骨壊死に対する口腔管理に関する研究	歯科口腔外科 中村康典
50	HTLV-1 感染症の発症リスクの解明に関する研究	腫瘍内科 魚住公治
51	甲状腺癌の分子標的薬による治療	腫瘍内科 魚住公治
52	爪部悪性黒色腫への指趾骨温存切除による新たな低侵襲標準治療の開発	皮膚腫瘍科・皮膚科 松下茂人
53	頭頸部基底細胞癌縮小マージン切除による新たな低侵襲標準治療の開発	皮膚腫瘍科・皮膚科 松下茂人
54	進行性悪性黒色腫治療における抗 PD-1 抗体との TM5614 の安全性・有効性を検討する第 II 相試験	皮膚腫瘍科・皮膚科 松下茂人
55	メラノサイト系の悪性腫瘍に関する角層解析の有用性	皮膚腫瘍科・皮膚科 松下茂人
56	急性皮膚潰瘍での創収縮のダイナミック解析と筋線維芽細胞の形態構築動態解析	皮膚腫瘍科・皮膚科 松下茂人
57	皮膚腫瘍における免疫応答解析に基づくがん免疫療法予測診断法の確立	皮膚腫瘍科・皮膚科 松下茂人
58	JCOG1309 病期 II 期および III 期皮膚悪性黒色腫に対するインターフェロン β 局所投与による術後補助療法のランダム化比較第 III 相試験	皮膚腫瘍科・皮膚科 松下茂人
59	JCOG1605：パクリタキセル既治療原発性皮膚血管肉腫に対するパゾパニブ療法の非ランダム化検証的試験	皮膚腫瘍科・皮膚科 松下茂人
60	ニボルマブ+イピリムマブで治療される悪性黒色腫患者における腸内細菌代謝産物の臨床的意義に関する前向き観察研究	皮膚腫瘍科・皮膚科 松下茂人
61	進行期悪性黒色腫疾患に対する術後補助療法後に関する観察研究	皮膚腫瘍科・皮膚科 松下茂人
62	粘膜型/末端黒子型メラノーマにおけるニボルマブ＋イピリムマブ併用療法の一次治療と抗 PD-1 抗体単剤療法の一次治療（無効後ニボルマブ＋イピリムマブを含む）の効果に関する多施設共同後ろ向き研究	皮膚腫瘍科・皮膚科 松下茂人
63	結合組織性皮膚疾患における病態解明	皮膚腫瘍科・皮膚科 松下茂人
64	悪性黒色腫における免疫チェックポイント阻害薬効果に対する HLA CLASS II の影響	皮膚腫瘍科・皮膚科 松下茂人
65	完全奏効(CR)患者における抗 PD-1 抗体治療中止後の効果持続についての後方視的研究	皮膚腫瘍科・皮膚科 松下茂人
66	進行期悪性黒色腫に対するニボルマブ・イピリムマブ併用療法の効果についての後ろ向き観察研究	皮膚腫瘍科・皮膚科 松下茂人
67	皮膚疾患画像ナショナルデータベースの構築と AI 活用診療支援システムの開発	皮膚腫瘍科・皮膚科 松下茂人

	研究内容・課題名	部署・研究者名
68	BRAF 陽性悪性黒色腫に対する BRAF・MEK 阻害薬および免疫チェックポイント阻害薬の臨床効果に関する多機関共同後ろ向き観察研究	皮膚腫瘍科・皮膚科 松下茂人
69	本邦における皮膚血管肉腫に対するタキサン系抗がん剤使用成績の検討：多施設共同観察研究	皮膚腫瘍科・皮膚科 松下茂人
70	悪性黒色腫のリンパ節郭清範囲に関する多施設共同観察研究	皮膚腫瘍科・皮膚科 松下茂人
71	乳房外パジェット病に対する S-1・ドセタキセル併用療法の効果についての後ろ向き観察研究	皮膚腫瘍科・皮膚科 松下茂人
72	末期腎不全患者に対する適切な腎代替療法の提供について	腎臓内科 古庄正英
73	Cryo AF グローバルレジストリ研究	不整脈治療科
74	非小細胞肺がんに対する免疫チェックポイント阻害剤とプラチナ製剤併用療法による免疫関連有害事象のリスク因子解析	薬剤部
75	骨シンチグラフィ解析ソフトウェアの研究・開発・評価等に関する研究	放射線科 杉尾浩
76	吸湿性繊維保護具を使用した場合のドレープ内の湿度温度および蒸れ感の変化	東 2 病棟 田中康
77	急性期病院の混合病棟で勤務する看護師の勤務継続につながる職務満足度因子の傾向	東 3 病棟 折田紋奈
78	看護師のリハビリテーションに対する認識とその影響因子	東 5 病棟 橋口未由紀
79	難治性腹水で KM－CART を実施した患者の身体症状に及ぼす苦痛や効果	東 6 病棟 井手口和絵
80	経カテーテル的大動脈弁置換術を受ける患者のフレイルに影響する要因分析	東 7 病棟 厚地美穂
81	循環器疾患患者のアドバンス・ケア・プランニング（ACP)の必要性に関する病棟看護師の認識	東 8 病棟 溝口準
82	骨髄異形成症候群の患者とエンド・オブ・ライフ・ディスカッションを行う看護師の構え	西 4 病棟 榊詩織
83	外回り看護師が手術中に個人防護具着用を徹底できない要因	手術室 砂坂志織
84	循環器外来における未受診患者の要因と分析	外来 井出之上涼子
85	学内で実施した精神看護学実習における看護学生の学び	看護学校 石原史絵
86	実習指導者会議における臨床判断モデルとリフレクションを活用した学習会の効果	看護学校 西元智子
87	看護学生の認知症高齢者に抱くイメージ	看護学校 星野睦美
88	看護学生の「子ども理解」に関する学年比較	看護学校 谷川仁美
89	九州管内の国立病院機構病院 28 施設に勤務する卒後 1～5 年目看護職の属性と看護実践能力との関連	看護学校 山田巧
90	重度心身障害児（者）病棟に勤務する看護職員の倫理観を高めるための看護管理者の実践	看護学校 髙木雅弘

② 治験実績

以下に 2021 年度の治験の実績を示す。

2021 年度(令和 3 年度)治験内容　　2021.4～2022.3

	医薬品		医療機器		再生医療		合計
	新規契約	継続契約	新規契約	継続契約	新規契約	継続契約	
治験　第Ⅱ相	1(0)	1(1)	0(0)	0(0)	0(0)	1(1)	3(2)
治験　第Ⅲ相	0(0)	3(5)	0(0)	0(1)	0(0)	0(0)	3(6)
合計	1(0)	4(6)	0(0)	0(1)	0(0)	1(1)	6(8)

(　)内は昨年の実数

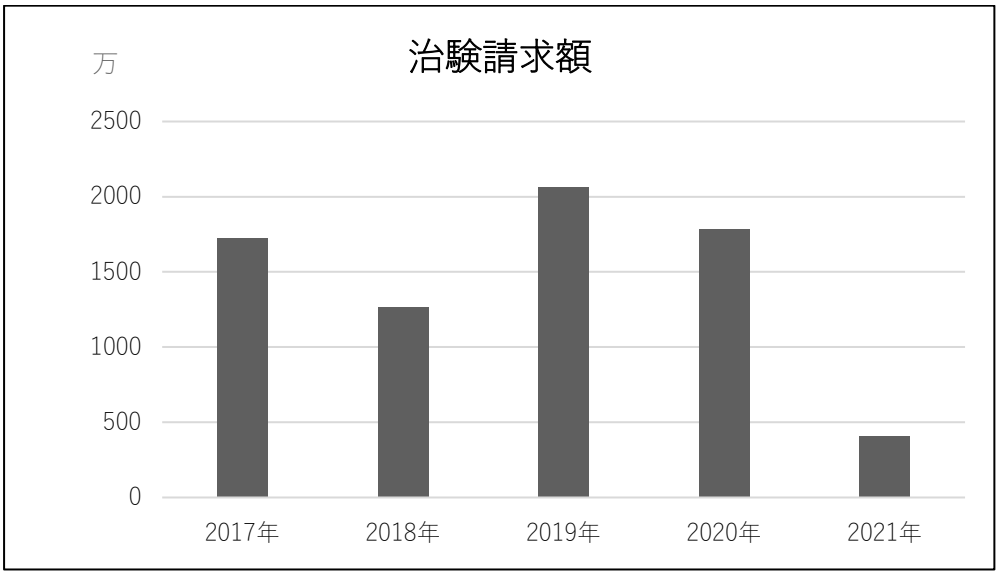
Ⅱ/Ⅲ相試験はⅡ相の項目に記載

実施率(2021 年度に終了した治験)

	契約件数(件)	契約症例・調査数	実施症例・調査票	実施率(%)
治験	4(3)	10(20)	10(13)	100(65)

(　)内は昨年の実数

治験請求額推移



（ア） 治験の細目

研究課題名	研究依頼者	責任医師
未治療の多発性骨髄腫患者を対象とした BMS-901608 の国内第 2 相臨床試験	ブリストル・マイヤーズ スクイブ株式会社	大塚眞紀
（再生医療等製品） 株式会社ヘリオスの依頼による脳梗塞患者を対象とした HLCM051 の第 II/III 相試験	株式会社ヘリオス	松岡秀樹
ゼリア新薬工業株式会社の依頼による子宮頸癌患者を対象としたZ-100 の第Ⅲ相試験	ゼリア新薬工業株式会社	大田俊一郎
第一三共株式会社の依頼による急性骨髄性白血病患者を対象としたキザルチニブ(AC220)の第Ⅲ相試験	第一三共株式会社	大塚眞紀
R788 の慢性特発性血小板減少性紫斑病患者を対象とした第 III 相臨床試験	キッセイ薬品工業株式会社	大塚眞紀
Elezanumab の前期第Ⅱ相試験	アッヴィ合同会社	松岡秀樹

（イ） 製造販売後調査

研究課題名	研究依頼者	責任医師
アデムパス錠 使用成績調査	バイエル薬品株式会社	蔡 榮鴻
オプジーボ点滴静注 使用成績調査 「根治切除不能な悪性黒色腫」	小野薬品工業株式会社	松下茂人
ゼルボラフ錠 240mg 特定使用成績調査	中外製薬株式会社	松下茂人
ゼルボラフ錠 240mg 特定使用成績調査	中外製薬株式会社	魚住公治
献血グロベニン-I静注用 使用成績調査（再審査用）「スティーブンス・ジョンソン症候群及び中毒性表皮壊死症」	日本製薬株式会社	松下茂人
ｵﾌﾟｽﾐｯﾄ錠 10m 特定使用成績調査(長期使用)	ヤンセンファーマ株式会社	塗木徳人
ビプリブ®点滴静注用 400 単位 使用成績調査	武田薬品工業株式会社	大塚眞紀
ジャカビ®錠 5mg 特定使用成績調査	ノバルティスファーマ株式会社	大塚眞紀
マリゼブ®錠 12.5mg, 25mg 特定使用成績調査（長期使用に関する調査）	MSD 株式会社	郡山暢之
レブラミド®カプセル 5mg, 2.5mg 特定使用成績調査 「未治療の多発性骨髄腫に対する有効性・安全性調査」	ブリストル・マイヤーズ スクイブ株式会社	大塚眞紀
ジャカビ®錠 5mg 特定使用成績調査（真性多血症）	ノバルティスファーマ株式会社	魚住公治
ｵﾌﾟｽﾐｯﾄ錠 10mg 特定使用成績調査(長期使用)	ヤンセンファーマ株式会社	田中裕治
アイノフロー吸入用 800ppm 使用成績調査	エア・ウォーター株式会社	金城玉洋
デュラグルチド（トルリシティ皮下注 0.75 mg アテオス） 特定使用成績調査	日本イーライリリー株式会社	郡山暢之
カイプロリス点滴静注用 10 ㎎,40 ㎎ 使用成績調査 「再発又は難治性の多発性骨髄腫に対する全例調査」	小野薬品工業株式会社	大塚眞紀
カイプロリス点滴静注用 10 ㎎,40 ㎎ 使用成績調査 「再発又は難治性の多発性骨髄腫に対する全例調査」	小野薬品工業株式会社	魚住公治
ベンテイビス 使用成績調査（PAH）	バイエル薬品株式会社	蔡 榮鴻

研究課題名	研究依頼者	責任医師
オプジーボ 特定使用成績調査〔再発又は難治性の古典的ホジキンリンパ腫〕	小野薬品工業株式会社	大塚眞紀
ムンデシンカプセル 100mg 特定使用成績調査	ムンディファーマ株式会社	大塚眞紀
レブラミド®カプセル 使用成績調査「再発又は難治性の成人 T 細胞白血病リンパ腫」	ブリストル・マイヤーズスクイブ株式会社	大塚眞紀
アイクルシグ錠 15mg 使用成績調査	大塚製薬株式会社	大塚眞紀
自家培養表皮ジェイスの先天性巨大色素性母斑に対する使用成績調査	株式会社ジャパン・ティッシュ・エンジニアリング	松下茂人
サデルガカプセル 100mg 特定使用成績調査	サノフィ株式会社	大塚眞紀
バベンチオ点滴静注 200mg 特定使用成績調査 （根治切除不能なメルケル細胞癌）	メルクバイオファーマ株式会社(IQVIA サービシーズジャパン株式会社)	松下茂人
ウプトラビ錠 0.2mg, 0.4mg 特定使用成績調査 「長期使用に関する調査」	日本新薬株式会社	田中裕治
ダラザレックス点滴静注 100mg, 400mg 特定使用成績調査（再発又は難治性の多発性骨髄腫）＜プロトコール No.DZX1L＞	ヤンセンファーマ株式会社	大塚眞紀
サビーン®点滴静注用 500mg 使用成績調査（全例調査）	キッセイ薬品工業株式会社	魚住公治
ベスポンサ®点滴静注用 1mg 特定使用成績調査（プロトコール No.:B1931024）	ファイザー株式会社	原口浩一
ラパリムスゲル 0.2% 一般使用成績調査(全例調査)-結節性硬化症に伴う皮膚病変-	ノーベルファーマ株式会社	松下茂人
レボレード錠 特定使用成績調査 （再生不良性貧血）	ノバルティスファーマ株式会社	大塚眞紀
献血ノンスロン 500 注射用・献血ノンスロン１５００注射用 アンチトロンビンⅢ低下を伴う門脈血栓症 使用成績調査	日本製薬株式会社	櫻井一宏
イストダックス®点滴静注用 10mg 使用成績調査「再発又は難治性の末梢性 T 細胞リンパ腫」	ブリストル・マイヤーズスクイブ株式会社	大塚眞紀
トラディアンス配合錠 特定使用成績調査（長期使用に関する調査）	日本ベーリンガーインゲルハイム株式会社	郡山暢之
ビラフトビ®・メクトビ®併用療法 特定使用成績調査〔BRAF 遺伝子変異を有する根治切除不能な悪性黒色腫〕	小野薬品工業株式会社	松下茂人
ゾスパタ錠 一般使用成績調査〔プロトコル No.XSP001〕	アステラス製薬株式会社	大塚眞紀
ヴァンフリタ錠 一般使用成績調査	第一三共株式会社	大塚眞紀
レパーサ皮下注 特定使用成績調査（長期使用）	アムジェン株式会社	片岡哲郎
レパーサ皮下注 特定使用成績調査（長期使用）	アムジェン株式会社	東 健作
デファイテリオ静注 200mg 一般使用成績調査	日本新薬株式会社	大塚眞紀
ジフォルタ®注射液 20 ㎎ 使用成績調査	ムンディファーマ株式会社	大塚眞紀
ベレキシブル®錠 特定 使用成績調査 再発又は難治性の中枢神経系原発リンパ腫（PCNSL）	小野薬品工業株式会社	魚住公治
サピエン 3（TAV in SAV）使用成績調査	エドワーズライフサイエンス株式会社	片岡哲郎
サピエン 3（TAV in SAV） 使用成績調査	エドワーズライフサイエンス株式会社	平峯聖久
コララン®特定使用成績調査（洞調律かつ投与開始時の安静時心拍数が 75 回/分以上の慢性心不全：ただし、β遮断薬を含む慢性心不全の標準的な治療を受けている患者に限る。）	小野薬品工業株式会社	中島 均

研究課題名	研究依頼者	責任医師
コララン® 特定使用成績調査 （洞調律かつ投与開始時の安静時心拍数が 75 回/分以上の慢性心不全：ただし、β遮断薬を含む慢性心不全の標準的な治療を受けている患者に限る。）	小野薬品工業株式会社	東　健作
ビンダケルカプセル 特定使用成績調査 ～トランスサイレチン型心アミロイドーシス患者に対する調査～ （プロトコール №B3461064）	ファイザー株式会社	薗田正浩
エドルミズ® 特定使用成績調査〔がん悪液質：非小細胞肺癌、胃癌、膵癌、大腸癌〕	小野薬品工業株式会社	魚住公治
ポライビー®点滴静注用 30 mg、同 140 mg 一般使用成績調査（全例調査）－再発又は難治性のびまん性大細胞型 B 細胞リンパ腫－	中外製薬株式会社	大塚眞紀
ポライビー®点滴静注用 30 mg、同 140 mg 一般使用成績調査（全例調査）－再発又は難治性のびまん性大細胞型 B 細胞リンパ腫－	中外製薬株式会社	魚住公治
Penumbra アスピレーションシステム 使用実態調査	株式会社メディコスヒラタ	濵田祐樹
ダラキューロ配合皮下注 ベルケイド注射用 3mg 全身性 AL アミロイドーシス患者を対象とした特定使用成績調査	ヤンセンファーマ株式会社	大塚眞紀
「リクシアナ OD 錠」に関する副作用詳細調査	第一三共株式会社	塗木徳人
ハイヤスタ錠®10mg 再発または難治性の成人 T 細胞白血病リンパ腫(ATL)患者における一般使用成績調査(全例調査)	Meiji Seika ファルマ株式会社	大塚眞紀
オプジーボ点滴静注 20mg・100mg・120mg・240mg、ヤーボイ点滴静注液 20mg・50mg 副作用・感染症詳細調査	小野薬品工業株式会社	青木恵美
コミナティ一筋注 一般使用成績調査（C4591006）「承認後早期に接種される被接種者（医療従事者）を対象とした追跡調査」	ファイザー株式会社	城ヶ崎倫久

3. 業績報告

① 英文原著論文等

※2021 年度中に Epub(online で公開)された論文も含みます。また、実際に印刷された年度に再掲載しています。鹿児島医療センター以外の所属で発表された論文も掲載しました。

■第1循環器内科

Kitagawa K, Nakamura S, Ota H, Ogawa R, Shizuka T, **Kubo T**, Yi Y, Ito T, Nagasawa N, Omori T, Nakamori S, Kurita T, Sugisawa J, Hatori N, **Nakashima H**, Wang Y, Kido T, Watanabe K, Matsumoto Y, Dohi K, Sakuma H.
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Michallek F, Nakamura S, Ota H, Ogawa R, Shizuka T, **Nakashima H**, Wang YN, Ito T, Sakuma H, Dewey M, Kitagawa K.
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■第2循環器内科

Hamadanchi A, **Ijuin S**, Haertel F, Bekfani T, Westphal J, Franz M, Moebius-Winkler S, Schulze PC.
A Novel Echocardiographic-Based Classification for the Prediction of Peri-Device Leakage following Left Atrial Appendage Occluder Implantation.
J Clin Med. 2022; 11(4): 1059.

■不整脈治療科

Fukata M, Yamasaki H, **Sai E**, Ogawa K, Kuroki K, Igarashi M, Sekiguchi Y, Kimura K, Seo Y, Odashiro K, Akashi K, Nogami A, Aonuma K.
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■小児科

Horigome H, Ishikawa Y, Takahashi K, **Yoshinaga M**, Sumitomo N.
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Suzuki H, Horie M, Ozawa J, Sumitomo N, Ohno S, Hoshino K, Ehara E, Takahashi K, Maeda Y, **Yoshinaga M**, Tateno S, Takagi J, Doi S, Hoshina S, Sato I, Ishikawa T, Makita N, Chinushi M, Akazawa K, Nagashima M.
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Yoshinaga M, Ishikawa S, Otsubo Y, Shida M, Hoshiko K, Yatsunami K, Kanaya Y, Takagi J, Takamura K, Ganaha H, Sunagawa M, Soeda O, Ogawa Y, Ogata H, Kashima N.
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Yoshinaga M, Horigome H, Ayusawa M, Yasuda K, Kogaki S, Doi S, Tateno S, Ohta K, Hokosaki T, Nishihara E, Iwamoto M, Sumitomo N, Ushinohama H, Izumida N, Tauchi N, Kato Y, Kato T, Chisaka T, Higaki T, Yoneyama T, Abe K, Nozaki Y, Komori A, Kawai S, Ninomiya Y, **Tanaka Y**, **Nuruki N**, **Sonoda M**, Ueno K, Hazeki D, Nomura Y, Sato S, Hirono K, Hosokawa S, Takechi F, Ishikawa Y, Hata T, Ichida F, Ohno S, Makita N, Horie M, Matsushima S, Tsutsui H, Ogata H, Takahashi H, Nagashima M.
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Loss-of-function mutations in cardiac ryanodine receptor channel cause various types of arrhythmias including long QT syndrome.
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■血液内科

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■糖尿病・内分泌内科

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■消化器内科

Ijuin S, Oda K, Mawatari S, Taniyama O, Toyodome A, Sakae H, Tabu K, Kumagai K, Kanmura S, Tamai T, **Moriuchi A**, Uto H, Ido A.
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■外科・消化器外科

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■病理診断科

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Yoshimura T, Higashi S, Yamada S, Noguchi H, **Nomoto M**, Suzuki H, Ishida T, Takayama H, Hirano Y, Yamashita M, Tanimoto A, Nakamura N.
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■歯科口腔外科

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■皮膚腫瘍科・皮膚科

Nakamura Y, Namikawa K, Yoshikawa S, Kiniwa Y, Maekawa T, Yamasaki O, Isei T, **Matsushita S**, Nomura M, Nakai Y, Fukushima S, Saito S, Takenouchi T, Tanaka R, Kato H, Otsuka A, Matsuya T, Baba N, Nagase K, Inozume T, Fujimoto N, Kuwatsuka Y, Onishi M, Kaneko T, Onuma T, Umeda Y, Ogata D, Takahashi A, Otsuka M, Teramoto Y, Yamazaki N.
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下田平佳純、木村菜美子、鞍掛奈津希、本庄希江、西　恭宏、中村康典
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松下茂人
教育講演 23「非メラノーマ皮膚悪性腫瘍の治療最前線」 基底細胞癌
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第 30 回日本形成外科学会基礎学術集会、東京、2021 年 10 月 7 日

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With コロナ時代の病診連携について
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青木恵美、松下茂人
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青木恵美、山村健太郎、蓑川葉子、坂本翔一、平野 唯、坂口郁代、松下茂人
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古庄正英、末吉 瞳、大毛夏菜子
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安庭愛子、馬籠さつき、馬場善政、松崎 勉
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金城多架良
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特定薬剤リストに基づく積極的疑義照会の活用
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九州国立病院機構診療放射線技師会学術大会、Web 開催、2021 年 9 月 25 日

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松井弓花、白石彩花、味園洋子
急性期病棟における身体抑制に対する看護師の意識の変化
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大迫朋子
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第 75 回国立病院総合医学会、仙台市、2021 年 10 月 22～23 日

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馬籠さつき
苦痛のスクリーニングシートの取り組みと現状
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大毛夏菜子、末吉 瞳
腹膜透析外来における看護師の役割
第 27 回日本腹膜透析医学会学術集会、東京都、2021 年 10 月 30～31 日

加藤崇志、田上さとみ、西岡恵子、堂園文子、池田智子、福迫直美、松本深雪
看護師が働き続けられる職場環境の検討
第 55 回鹿児島県保健看護研究学会、鹿児島、2022 年 1 月 22 日

久保彩香、江内谷彩香、清水優一、藤崎佑貴子、東 美希、久保田詳子
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第 55 回鹿児島県保健看護研究学会、鹿児島、2022 年 1 月 22 日

深野久美、山田 巧、大野美穂
コロナ禍における臨地実習の経験と卒業時の看護実践能力の自信度の関係
第 19 回国立病院看護研究学会学術集会、東京、2021 年 12 月 11 日

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九州内の国立病院機構病院 28 施設に勤務する卒後 1～5 年目看護職の看護実践能力～国立病院機構附属養成所とその他の教育課程との比較～
第 75 回国立病院総合医学会学術集会、仙台、2021 年 10 月 23 日

谷川仁美、山田 巧、澁谷幸子、今田南生人
看護学生の「子ども理解」に関する学年別比較の特徴
第 75 回国立病院総合医学会学術集会、仙台、2021 年 10 月 23 日

筆頭演者が鹿児島医療センターの職員以外

＜国内学会＞

鈴木 甫、高山大生、吉村卓也、手塚征宏、東 翔太朗、田中孝明、福永 香、網谷真理恵、網谷東方、
改元 香、渡邉里美、榎本 孝、山中寿和、日高直人、下川昭代、中村康典、油田幸子、今村也寸志、
石部良平、中村典史
「種子島スタディ」口腔から種子島市地域高齢者の健康長寿延命につなげる包括的高齢者機能評価（第 1 報）
第 18 回日本口腔ケア学会・学術大会、東京（Web 開催）、2021 年 4 月 18 日

福永 香、吉村卓也、鈴木 甫、手塚征宏、東翔太朗、高山大生、田中孝明、中村康典、石部良平
川内市医師会立川内市民病院における口腔ケアに対する意識改善への取り組み
第 18 回日本口腔ケア学会・学術大会、東京（Web 開催）、2021 年 4 月 17 日～5 月 16 日

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irAE マネジメント強化に向けた施設間連携(鹿児島がん免疫療法サポートネットワーク：KISNet の評価に関するアンケート調査)
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鈴木寛人、津曲恭一、山形真一
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鈴木寛人、平田亮介、簗田晃直、上原智博、津曲恭一、仲本 敦、河崎英範、渡嘉敷崇、山形真一
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濵田祐樹
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東　健作
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東　健作
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松岡秀樹
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松岡秀樹
鹿児島県における病診連携の取り組みと脳卒中予防
脳卒中二次予防連携セミナー、鹿児島（Web）、2021 年 6 月 1 日

松岡秀樹
心原性脳塞栓症の最新治療
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松岡秀樹
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松岡秀樹
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松岡秀樹
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松下茂人
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松下茂人
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松下茂人
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松下茂人
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松下茂人
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古庄正英
PD 関連感染症を最小化するための戦略的システム構築
テルモ PD 学術講演会、長崎市(web)、2021 年 9 月 7 日

古庄正英
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古庄正英
他疾患併存時代の腎疾患診療
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古庄正英
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第 13 回宮崎県腹膜透析研究会、宮崎、2022 年 3 月 20 日

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⑥ 論文

当院所属で筆頭者として発表された論文を掲載します。

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CASE REPORT

Prosthetic vascular graft rupture caused by claw-type rib fixation strut: a case report

Akira Hiwatashi[1] · Kosuke Mukaihara[1] · Kazuya Terazono[1] · Shuji Nagatomi[1] · Yuta Shiramomo[1] · Naoki Tateishi[1] · Tamahiro Kinjo[1] · Hitoshi Nakashima[2] · Junichi Ideue[3] · Yoshiharu Soga[4]

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Abstract
A 66-year-old-man who had undergone partial aortic arch and descending aortic graft replacement for a dissecting aortic aneurysm presented to our hospital with pain and beating swelling of his left back shoulder. Enhanced computed tomography and aortic angiography revealed graft rupture caused by one of the claws of a rib fixation strut. Furthermore, another claw had invaded a lung. We performed emergency thoracic endovascular aortic repair, and removed all of the struts 3 weeks later. Claw-type rib fixation struts have the potential to injure other organs, including prosthetic grafts. Careful follow-up is mandatory after implantation of this type of strut.

Keywords Rib fixation strut · Graft rupture · Bleeding · Aorta · Endovascular aortic repair

Introduction

Surgical rib fixation using metal struts has been shown to reduce days of ventilation, ICU stay, and medical cost in patients with severe flail chest. The Judet-like strut (KANI, USCI, Tokyo, Japan) is a claw-type rib fixation strut that has been reported to be useful for not only flail chest patients, but also patients who have undergone rib-cross thoracotomy (Fig. 1). Non-anastomotic rupture of a prosthetic vascular graft due to mechanical stress is a rare and potentially lethal condition. We herein report a case in which a KANI strut caused the rupture of a woven Dacron prosthetic vascular graft 2 years after replacement of the partial aortic arch and descending aorta.

✉ Akira Hiwatashi
a.hiwatashi@outlook.com

1 Department of Cardiovascular Surgery, Kagoshima Medical Center, 8-1 Shiroyama-cho, Kagoshima, Kagoshima 892-0853, Japan

2 Department of Cardiology, Kagoshima Medical Center, 8-1 Shiroyama-cho, Kagoshima, Kagoshima 892-0853, Japan

3 Department of Radiology, Kagoshima Medical Center, 8-1 Shiroyama-cho, Kagoshima, Kagoshima 892-0853, Japan

4 Department of Cardiovascular Surgery, Kagoshima University, 8-35-1 Sakuragaoka, Kagoshima, Kagoshima 890-8520, Japan

Case

A 66-year-old-man was transferred to our institution from an outside facility with complaints of pain and beating swelling of his left back shoulder (Fig. 2). Two years previously he had undergone replacement of the partial aortic arch and descending aorta from the proximal left subclavian artery to the diaphragm with a woven Dacron vascular graft (J graft SHIELD NEO®, Japan Lifeline, Tokyo, Japan) due to dissecting aortic aneurysm. The 5th and 6th ribs had been transected on both the front and back sides, and the 7th rib had been transected on the front side in left lateral thoracotomy. Five KANI struts had been applied to fix the ribs. One year previously, he had noticed swelling of the left shoulder. The site of swelling had been growing and beating, and he had experienced hoarseness for 2 weeks. On examination, his vital signs were within the normal limits. Computed tomography (CT) (Fig. 3) and aortic angiography revealed a massive subfascial hematoma with active bleeding from the main body of the prosthetic graft. The two bleeding points corresponded with the pair of claws of one of the KANI struts. Furthermore, another claw had invaded the lung. The condition was diagnosed as a vascular graft rupture and lung injury caused by a change in the shape of the claws of KANI struts. Endovascular stent grafting was immediately performed, which stopped the bleeding (Fig. 4). At 3 weeks after the operation, we removed all struts and repaired the

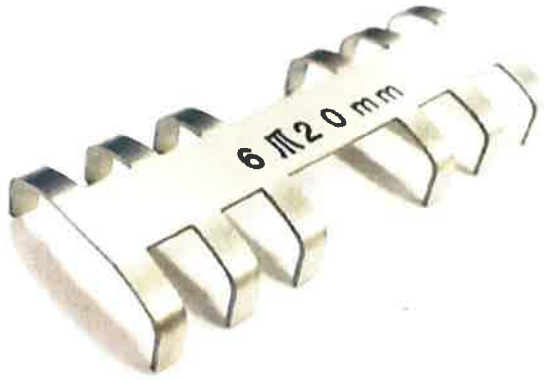

Fig. 1 KANI is made from titanium. Five types of widths (16–24 mm) are available

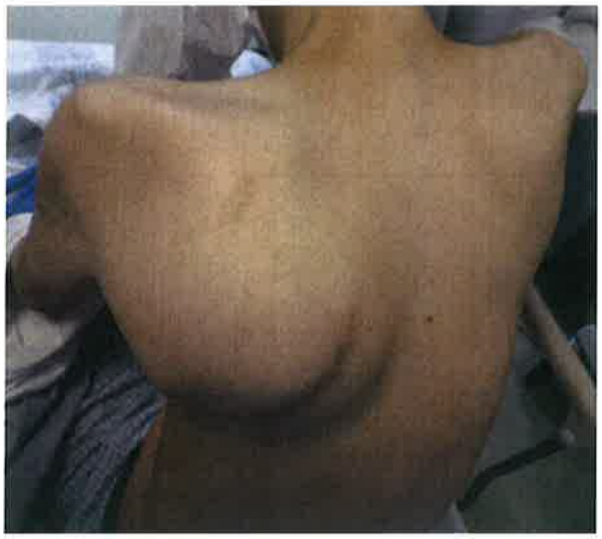

Fig. 2 Photograph showing the swelling on the left back shoulder

lung injury to prevent re-injury of the vascular graft and lungs (Fig. 5a). When the KANI struts were removed, part of the nitinol stent and fabric were observed in a hole in the vascular graft, located near to the protruding claw (Fig. 5b). There was no bleeding after removal following successfully sealing using a stent graft. The patient had an uneventful postoperative course.

Discussion

The claw-type rib fixation plate was introduced by Judet in 1973. Judet struts are made of stainless steel. The KANI, which is made from titanium, came into use in 1993. Previous studies have shown that the use of KANI struts has good

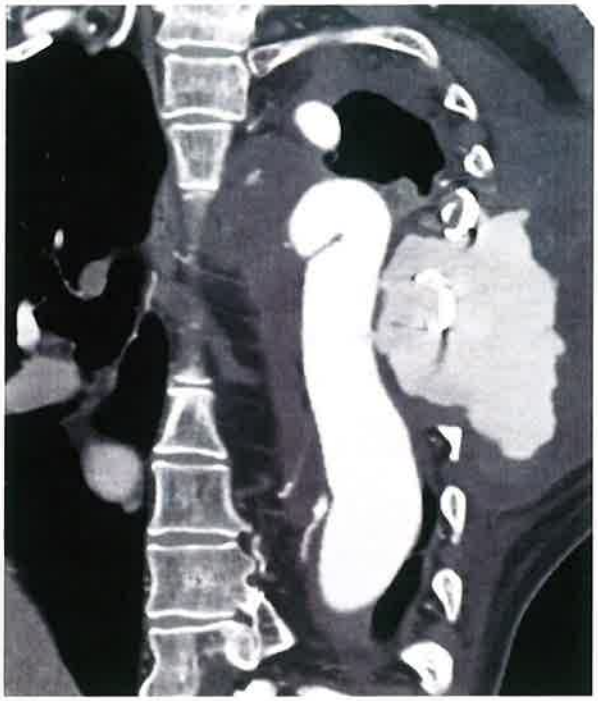

Fig. 3 A coronal plane of preoperative CT showed that the two bleeding points corresponded with pair of claws of the KANI struts for the 6th cross-rib

Fig. 4 CT 1 month after the endovascular stent grafting. There was no bleeding but the spontaneous resolution moved the KANI strut closer to the stent graft

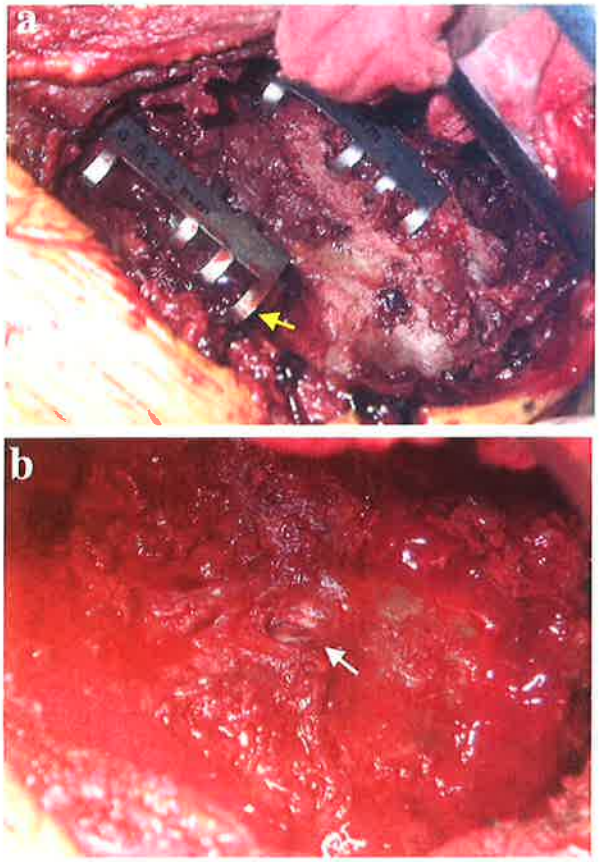

Fig. 5 Operative findings. **a** The claws of the KANI strut for the 6th cross-rib was straighten up. **b** A part of the stent and the fabric appeared in the hole defect of the vascular graft

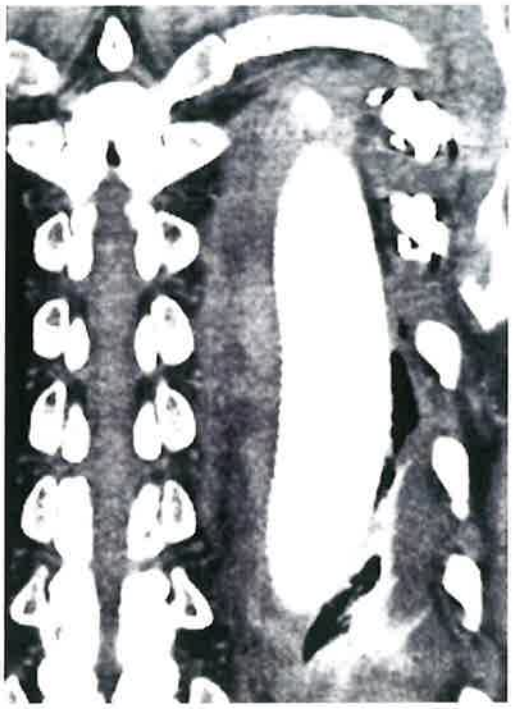

Fig. 6 Postoperative CT performed 11 days after partial aortic arch and descending aorta replacement. The configuration of the KANI struts and the prosthetic graft prior to the rupture are shown. The claws of KANI struts had been molded and had not been straightening

effects for flail chest patients and patients who have undergone left-rib-cross thoracotomy [1, 2]. However, the KANI strut can lead to catastrophic complications by protruding into the pleural cavity. Ryomoto et al. reported a case in which the claw of a KANI strut injured the surface of the left ventricle and caused cardiac tamponade after descending aortic replacement through left rib-cross thoracotomy [3]. Although cutting ribs at the posterior site is a routine method in left thoracotomy, as it provides a wide view of the thoracic aorta, the rib stumps always come close to the prosthetic vascular graft because of the anatomical position. Surgeons should be aware of the possibility that, in rare cases, the rib stumps or rib fixation plates can cause the non-anastomotic rupture of the prosthetic vascular graft due to mechanical stress.

In our case, the KANI strut for the 6th cross-rib was close to the point at which the prosthetic vascular graft ruptured. The claws of the KANI struts had been molded around the bilateral edges of the ribs in accordance with the usual recommended procedure, and had not been straightening, based on postoperative CT (Fig. 6). However, we confirmed that the claws were straightening. We assumed that the respiratory fluctuation caused the claws to gradually straighten while the transected ribs were not completely healed. Since the tips of the claws are dull, we presumed that continuous and frequent contact caused by arterial pulsation and respiratory fluctuation between the straightened claw and the prosthetic vascular graft caused rupture. Although we could obtain good early results by endovascular stent grafting, we were concerned about re-bleeding due to mechanical stress between the KANI struts and the stent graft. We, therefore, removed all five of the struts, including the strut that had invaded the lung.

The treatment strategy was considered to be appropriate because the tip of the straightened claws were very close to the exposed stent graft. Heart and great vessel injury should be avoided because it is a lethal complication. A careful

follow-up is indispensable in cases of KANI struts were used for fixing ribs with left thoracotomy.

Conclusion

KANI struts have the potential to injure other organs including prosthetic grafts. Surgeons should pay attention to this fact and careful follow-up is necessary for patients who undergo implantation of KANI struts.

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Original Article

Sudden out-of-hospital cardiac arrest in pediatric patients in Kyushu area in Japan

Masao Yoshinaga,[1] Shiro Ishikawa,[2] Yoshikazu Otsubo,[3] Masanori Shida,[4] Kiyomi Hoshiko,[3] Koichi Yatsunami,[5] Yoshiaki Kanaya,[6] Junichi Takagi,[7] Kazushi Takamura,[7] Hitoshi Ganaha,[8] Makoto Sunagawa,[8] Osamu Soeda,[2] Yumi Ogawa,[1] Hiromitsu Ogata[9] and Naoko Kashima[1]

[1]Kagoshima Medical Association, Kagoshima, [2]Fukuoka Medical Association, Fukuoka, [3]Nagasaki Medical Association, Nagasaki, [4]Saga Medical Association, Saga, [5]Kumamoto Medical Association, Kumamoto, [6]Oita Medical Association, Oita, [7]Miyazaki Medical Association, Miyazaki, [8]Okinawa Medical Association, Naha, [9]Epidemiology and Biostatistics, Kagawa Nutrition University, Sakado, Japan

Abstract ***Background*:** It is well-known that a neurologically favorable outcome of out-of-hospital cardiac arrest (OHCA) is associated with the presence of bystander-initiated cardiopulmonary resuscitation (bystander CPR) and use of an automated external defibrillator. However, little is known about the effect of the presence of pre-existing conditions, prior activity, and locations on the outcome of pediatric OHCA.

***Methods*:** We analyzed the data from questionnaires about pediatric patients with OHCA aged from 3 days to 19 years in the Kyushu area in Japan between 2012 and 2016.

***Results*:** A total of 594 OHCA cases were collected. The numbers of OHCA cases and the rate of 1 month survival with a favorable neurological outcome during sleeping, swimming / bathing, and exercise were 192 (1.0%), 83 (32.5%), and 44 (65.9%), respectively. When an OHCA occurred at school (n = 56), 88% of children / adolescents received bystander CPR, but when it occurred at home (n = 390), 15% received bystander CPR. Cardiovascular (n = 61), suicide (n = 61), and neurological / neuromuscular (n = 44) diseases were three major pre-existing conditions. The OHCA of cardiovascular disease was associated with exercise (24/61) and mainly occurred at school (22/61). The OHCA of neurological / neuromuscular disease was associated with swimming/bathing (15/44) and mainly occurred during bathing at home (12/44). Multivariate regression analysis showed that the presence of bystander CPR ($P < 0.001$) and occurrence of OHCA at school ($P < 0.001$) were independently predictive of a favorable outcome in pediatric OHCA.

***Conclusion*:** The outcome was different among pre-existing conditions, prior activity, and location of OHCA. These findings might be useful for preventing OHCA and improving the outcome of pediatric OHCA.

Key words cardiopulmonary resuscitation, child, exercise, out-of-hospital cardiac arrest, school.

Out-of-hospital cardiac arrest (OHCA) in infants, children, and adolescents is an uncommon, but devastating, event that has an enormous effect not only family members but on the local community. Approximately 1800 OHCAs occur annually in children and adolescents who are aged <20 years in Japan.[1] The outcome of pediatric OHCA varies among reports. Previous reports have shown that a neurologically favorable outcome is associated with older age, shockable first rhythm, presence of bystander-initiated cardiopulmonary resuscitation (bystander CPR), use of an automated external defibrillator (AED), and high parental education.[2–11]

Correspondence: Masao Yoshinaga, MD PhD, Department of Pediatrics, National Hospital Organization Kagoshima Medical Center. Kagoshima, 892-0853, Japan.
Email: Yoshinaga.masao.ks@mail.hosp.go.jp

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Temporal trends in survival or a favorable neurological outcome are also different among reports. No temporal trends in survival rates were present in overall pediatric OHCA cases from 2005–2007 to 2011–2013[9] or from 2007 to 2012[10] in the USA. In contrast, survival with a favorable neurological outcome significantly improved in school-aged children and adolescents between 2005 and 2014[12] in Japan. A published executive summary indicated that the links in the infant and child Chain of Survival include prevention of conditions leading to cardiopulmonary arrest, in addition to early cardiopulmonary resuscitation, early activation of the emergency medical service system, early advanced life support, and skilled post-cardiac arrest / postresuscitation care.[13] In other words, prevention of the conditions leading to cardiopulmonary arrest is one of the important strategies to reduce the prevalence of pediatric OHCA. However, little is known about those conditions, namely the effect of the presence of known

pre-existing disease / health conditions (pre-existing conditions), prior activity, and location in detail in each case that might relate to the outcome of pediatric OHCA. This information could help establish new strategies to prevent or to improve the outcome of pediatric OHCA.

A committee on school-based cardiovascular (CV) screening in the young was developed by the Kyushu Medical Association in 1969 in Japan. This committee started surveillance of all causes of OHCA in those aged <20 years old in Kyushu area to determine the rate of OHCA that occurred in school, during exercise, and in subjects with pre-existing conditions among all causes of OHCAs from 2012.

The present study therefore aimed to examine the effect of pre-existing conditions, prior activity, and OHCA location in detail on the outcome of infants, children, and adolescents with OHCA in the Kyushu area of Japan. We also aimed to determine predictive factors associated with a favorable neurological outcome.

Methods

Study design and setting

The study is an ongoing retrospective, observational study by the Kyushu Medical Association. Kyushu is one of eight regions in Japan and consists of eight prefectures, with a population of approximately 14.4 million. The Kyushu Medical Association started to collect data for each patient with OHCA who was <20 years old from local fire departments, school doctors, and school boards in the Kyushu area since 2012. The study was approved by the ethics committee of the National Hospital Organization Kagoshima Medical Center.

Each prefectural medical association sent out questionnaires in April to gather information about pediatric OHCAs that occurred from January to December in the previous year. The questionnaires requested information on age, sex, presence or absence of pre-existing conditions and the name of the pre-existing conditions if present, time of a day, day of week, arrest location, prior activity just before OHCA, presence or absence of bystanders, bystander CPR, AED use, AED shockable, and outcome. Finally, the questionnaires asked for a detailed description of each case about prior activity and changes in the condition of the subject after CPR. Cardiac arrest was defined as cessation of cardiac mechanical activity as determined by the absence of signs of circulation.

The inclusion criterion of the present study was pediatric patients with OHCA aged from 3 days to 19 years. Exclusion criteria were subjects in whom cardiac arrest was not fully identified or the outcome was not described.

Classifications

Subjects were classified as infants (<1 year), preschool children (1–5 years), elementary school children (6–11 years), and adolescents (12–19 years). Arrest location in detail was classified into three categories of at school, outside school and home, and at home. Prior activity was categorized as sleeping, exercise-related, swimming / bathing, at rest, suicide, accidents that include traffic, fall, and fire accidents, miscellaneous, and unknown causes. Prior activities were defined as follows: sleeping, activity to rest one's body and mind with one's eye closed and not awake; exercise-related, during physical activity or after physical activity; swimming / bathing, during swimming in pool, river, or sea and during bathing in house; at rest, during doing anything tiring and not asleep.

Actual number of cases of OHCA that occurred in Kyushu area

The data for the actual OHCA cases that occurred in subjects aged <20 years between 2012 and 2016 in the Kyushu area were obtained from the Fire and Disaster Management Agency (FDMA) in Japan.[1]

Main outcome measures

The primary outcome measure was 1 month survival with a favorable neurological outcome, which was defined as Glasgow–Pittsburgh Cerebral Performance Category (CPC) 1 (good performance) or 2 (moderate disability).[3–5] The questionnaires requested information on outcome using the CPC scale since 2015. Between 2012 and 2014, the questionnaires requested information on outcome as alive, including the presence or absence of complications, dead, or unclear. The data and additional descriptions about changes in the condition of the subjects after CPR enabled us to classify subjects on the basis of whether they had a favorable outcome.

Statistical analysis

Differences in the rate of a favorable outcome among age groups were determined by ANOVA and the Tukey test. Differences in the rate of a favorable outcome between two

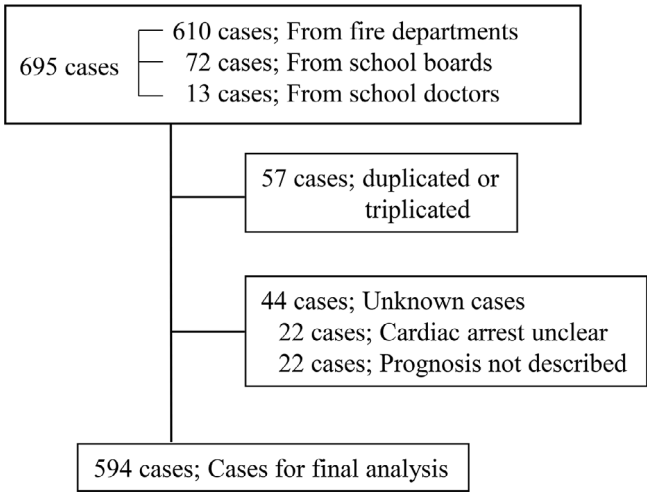

Fig. 1 Study selection process. Flowchart showing selection of cases for inclusion in the final study cohort.

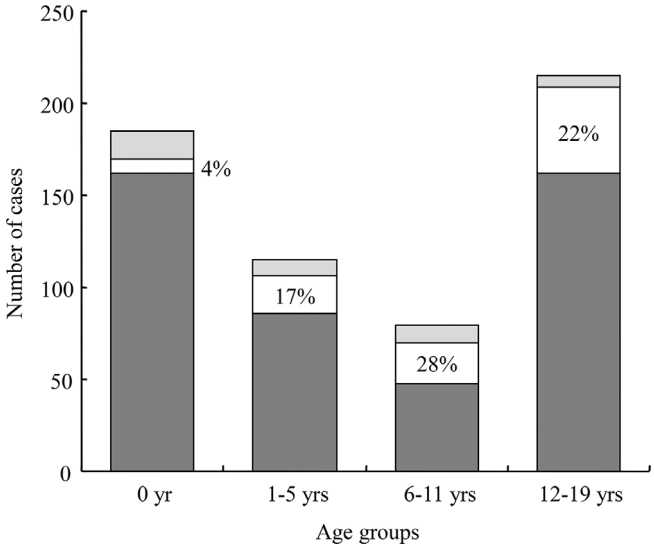

Fig. 2 The distribution of out-of-hospital cardiac arrest (OHCA) cases in each age group. Subjects were classified as infants (<1 year), preschool children (1–5 years), elementary school children (6–11 years), and adolescents (12–19 years). Numerals depict percentages of a neurologically favorable outcome (CPC1/2) in each age groups (b). Infants showed the highest rate of OHCA among all ages (a) and the rate of OHCA with a favorable outcome was the lowest in infants among four age groups. Abbreviations: CPC1/2, cerebral performance categories 1 or 2; CPC3-5, cerebral performance categories 3 to 5. (□), Unknown; (□), CPC1/2; (■), CPC3-5.

Table 1 Characteristics of subjects according to age groups (N=594)

Characteristics	0 year	1–5 years	6–11 years	12–19 years	Trend *P*	Total
No of subjects	185 (31%)	115 (19%)	79 (13%)	215 (36%)		594 (100%)
CPC 1/2†	8 (4%)	20 (17%)*	22 (28%)	47 (22%)	<0.001	97 (16%)
Male/female	101/84	76/39	44/35	142/73	0.05	363/231
CPC 1/2 (male)†	4 (4%)	16 (21%)*	12 (27%)	32 (23%)	<0.001	64 (18%)
CPC 1/2 (female)†	4 (5%)	4 (10%)	10 (29%)	15 (21%)	0.001	33 (14%)
Pre-existing condition‡	25 (14%)	52 (45%)	41 (52%)	133 (62%)	<0.001	251 (42%)
CPC 1/2†	2 (8%)	3 (6%)	10 (24%)	32 (24%)	0.02	47 (19%)
Witnessed	19 (10%)	38 (33%)	41 (52%)	85 (40%)	0.13	183 (31%)
CPC 1/2†	7 (37%)	17 (45%)	21 (51%)	41 (48%)	0.77	10 (47%)
Bystander-CPR‡	19 (10%)	41 (36%)**	40 (51%)	72 (33%)*	<0.001	172 (29%)
CPC 1/2†	8 (42%)	19 (46%)	22 (55%)	44 (61%)	0.38	93 (54%)
AED used‡	46 (25%)	44 (38%)	32 (41%)**	101 (47%)	<0.001	223 (38%)
CPC 1/2†	0	2 (5%)	12 (38%)	36 (36%)	<0.001	50 (22%)
AED shockable‡	0	4 (3%)	16 (20%)	43 (20%)	<0.001	63 (11%)
CPC 1/2†	0	1 (25%)	6 (38%)	23 (53%)	0.69	30 (48%)
OHCA at home‡	178 (96%)	84 (73%)	30 (38%)	97 (45%)	<0.001	389 (65%)
CPC 1/2†	7 (4%)	8 (10%)	2 (7%)	7 (7%)	0.37	24 (6%)
OHCA at school‡	-	-	16 (20%)	40 (19%)	-	56 (9%)
CPC 1/2†	-	-	14 (88%)	28 (70%)	-	42 (75%)

*$P < 0.01$. **$P < 0.001$. †Data are expressed as the number of subjects (%) (number of subjects with a favorable outcome)/(number of subjects in each group). ‡Data are expressed as the number of subjects (%) (number of subjects)/(number of subjects in each group). Statistical analysis was performed using ANOVA and the Tukey test. When significance was present between two age groups, an asterisk is shown by the latter age group. AED, automated external defibrillator; CPC1/2, cerebral performance categories 1 or 2; CPR, cardiopulmonary resuscitation; OHCA, out-of-hospital cardiac arrest; Pre-existing condition, known pre-existing disease/health condition.

groups were analyzed using Fisher's exact probability test. Predictive factors for a favorable outcome after OHCA were determined by multivariate logistic regression analysis. Univariate logistic regression analysis was initially performed using a favorable outcome as the dependent variable, and age, sex, presence or absence of pre-existing conditions, prior activity, arrest location, presence or absence of bystander CPR, AED use, and AED shockable as independent variables. Multivariate logistic regression analysis was then performed using variables that were identified as significant in univariate analysis. Statistical analyses were performed using IBM® SPSS® Statistics Version 23.0 (IBM Japan, Ltd., Tokyo, Japan). A two-tailed probability of <0.05 was considered statistically significant.

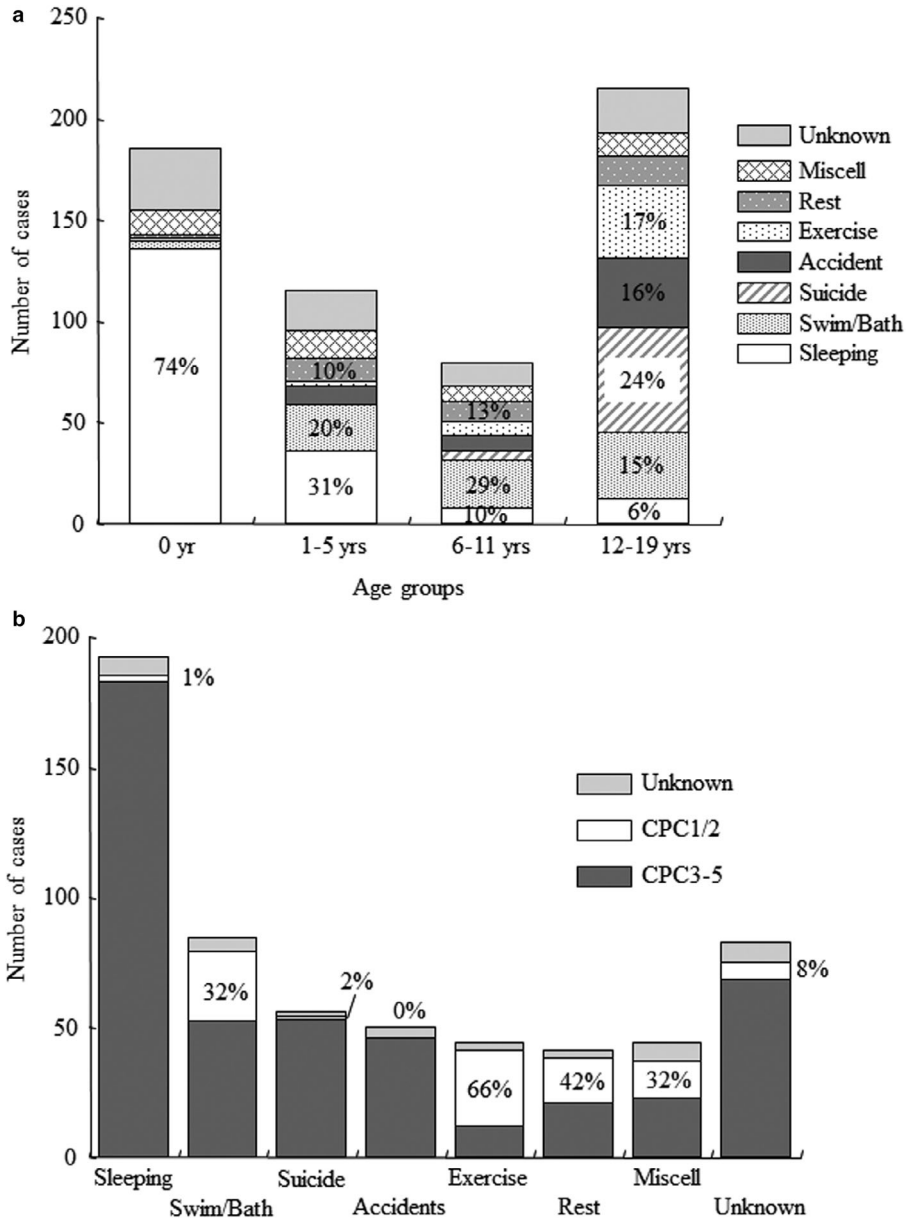

Fig. 3 Prior activity of OHCA by age group (a) and the outcome by etiology/prior activity of OHCA (b). Numerals depict percentages of prevalent etiology/prior activity in each age group (a) and a neurologically favorable outcome (CPC1/2) in each etiology/prior activity (b). Abbreviations: CPC1/2, cerebral performance categories 1 or 2; CPC3-5, cerebral performance categories 3 to 5.

Results

Patients

A total of 695 pediatric patients were obtained between January 2012 and December 2016. Of these, 610 reports were obtained from local fire departments, 72 from school boards, and 13 from school doctors (Fig. 1). We excluded a total of 101 cases. Of these, 57 cases that were reported in duplicate or in triplicate were excluded. We excluded another 44 cases as follows: 22 with no obvious signs of cardiac arrest; and 22 with no outcome described. The total number of 594 OHCA cases in the present study corresponded to 46.0% of actual cases that occurred in Kyushu area between 2012 and 2016. The distribution of age in the present study (Fig. 2) is similar to the data from the FDMA in Japan (Fig. S1).

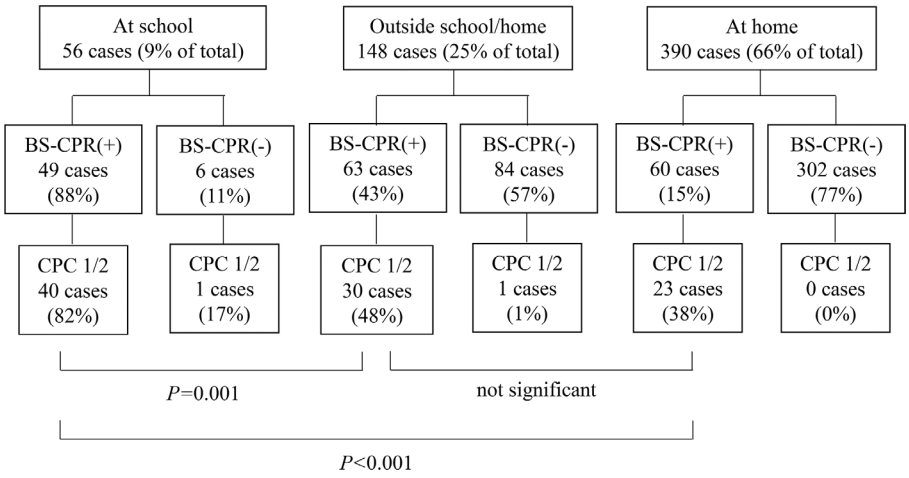

Fig. 4 Differences in outcome among locations and between the presence or absence of bystander-initiated cardiopulmonary resuscitation. Statistical analysis was performed with the Tukey test. Abbreviations: BS-CPR, bystander-initiated cardiopulmonary resuscitation.

Characteristics of pediatric OHCA

A final total of 594 cases was analyzed. Infants showed the highest rate of OHCA (185/594, 31.1%) among all ages (Table 1, Fig. 2). The rate of OHCA with a favorable outcome was low in infants (8/185, 4.3%) and high in elementary school children (22/79, 27.8%) among the four age groups (Fig. 2). The rate of OHCA was higher in boys than in girls in all ages. The presence of pre-existing conditions and a favorable outcome among patients with pre-existing conditions increased by age group. An upward trend was present in the rate of bystander CPR, AED use, and shockable AED by age group.

Prior activity in overall cases and outcome

The prevalent prior activity in each age group was as follows (Fig. 3a); during sleeping (136/185, 73.5%) in infants; during sleeping (36/115, 31.3%) and swimming/bathing (23/115, 20.0%) in preschool children; swimming/bathing (23/79, 29.1%) and at rest (10/79, 12.7%) in elementary school children; and suicide (52/215, 24.2%), exercise-related (36/215, 16.7%), accidents (34/215, 15.8%), and swimming/bathing (33/215, 15.3%) in adolescents.

The rates of favorable outcomes were high in exercise-related OHCA (29/44, 65.9%) (Fig. 3b). In contrast, the rates of favorable outcomes were low in accidents (0/52, 0%), during sleeping (2/192, 1.8%) and suicide (1/57, 1.8%). Among swimming/bathing cases, OHCA that occurred in the bathroom at home showed a significantly lower favorable outcome (6/33, 18.2%) than OHCA that occurred during swimming (21/50, 42.0%, $P = 0.03$).

Associations between location or the presence of bystander CPR and outcome

There was a close relationship among the location, the presence of bystander CPR, and the outcome. The rate of the presence of bystander CPR at school was significantly higher than that outside school/home ($P < 0.001$), and that outside school / home was significantly higher than that at home ($P < 0.001$) (Fig. 4). The rate of a favorable outcome was also significantly higher at school than that outside school / home or at home ($P = 0.001$ and $P < 0.001$, respectively).

Prior activity in subjects with pre-existing conditions and outcome

Of 594 subjects, 251 had pre-existing conditions (Table 2). Cardiovascular disease ($n = 61$), psychiatric / behavioral diseases ($n = 61$), and neurological / neuromuscular disease ($n = 44$) were major pre-existing conditions. Congenital heart disease, arrhythmia, and cardiomyopathy / myocarditis were prevalent in CV disease. Epilepsy was the most frequent condition in neurological / neuromuscular disease. The rate of a favorable outcome in CV disease (27/61, 44.3%) was significantly higher than that in neurological / neuromuscular disease (7/44, 15.9%, $P = 0.003$) (Fig. 5a).

With regard to prior activities, exercise was most frequent in subjects with CV disease (24/61, 39.3%) (Fig. 5b), particularly in those with arrhythmias (9/14, 64.3%) and cardiomyopathy / myocarditis (7/12, 58.3%). However, the rate of a favorable outcome was high (9/9, 100%) in subjects with arrhythmias, but it was low (4/7, 57.1%, $P = 0.06$) in those with cardiomyopathy / myocarditis.

In subjects with neurological / neuromuscular disease, swimming / bathing (15/44, 34.1%) was the most frequent etiology. In particular, 13 of 21 (61.9%) subjects with epilepsy experienced OHCA during bathing at home ($n = 11$) or swimming (one each in the school pool and in the river) and none had a favorable outcome (0/13, 0%).

Associations among pre-existing conditions, locations, the presence of bystander CPR, and outcome

Differences in location and in the rate of presence of bystander CPR affected the outcome of subjects with pre-existing

Table 2 Known pre-existing disease/health conditions (N=251)

Names of pre-existing conditions	No†	No‡	No§
Cardiovascular diseases	61		
Congenital heart diseases		15	
Arrhythmia		14	
Catecholaminergic polymorphic VT			4
WPW syndrome			3
Cardiomyopathy/myocarditis		12	
Hypertrophic cardiomyopathy			9
Past history of syncope¶		4	
Miscellaneous		4	
Unspecified		12	
Psychiatric / behavioral diseases††	61		
Neurological / neuromuscular diseases	44		
Epilepsy			21
Hydrocephalus			5
Muscular dystrophy			4
Spinal muscular atrophy			3
Miscellaneous			9
Severe motor and intellectual disabilities	24		
Cerebral palsy			10
Encephalopathy			3
Miscellaneous			15
Chromosomal aberration	18		
21 Trisomy		4	
18 Trisomy		3	
13 trisomy		3	
Miscellaneous		5	
Unspecified		3	
Respiratory diseases	16		
Asthma			8
Miscellaneous			4
Unspecified			4
Miscellaneous	27		
Total	251		

†No; Number of patients with large categories like cardiovascular diseases. ‡No; Number of patients with subcategories like arrhythmia. §No; Number of patients with each disease. ¶The etiology of syncope was not specified. "Past history of syncope" was arbitrarily included in the category of cardiovascular diseases. ††OHCA cases due to suicide were included in the category of psychiatric / behavioral diseases. VT, ventricular tachycardia.

conditions. Subjects with CV disease experienced OHCA at school (22/61, 36.1%), outside school/home (16/61, 26.2%), and at home (23/61, 37.7%). When OHCA occurred at school, 20 of 22 (90.9%) subjects received bystander CPR and 16 of 20 (80.0%) subjects showed a favorable outcome. When OHCA occurred at home (n = 23), seven (30.4%) subjects received bystander CPR and three of seven patients showed a favorable outcome. In subjects with 62 psychiatric / behavioral diseases, 57 cases were due to suicide; 47 cases occurred at home, nine cases outside school and home, and one case at school. Subjects with neurological/neuromuscular disease experienced OHCA mostly at home (30/44, 68.2%). Among them, only six (20.0%) subjects received bystander CPR and one showed a favorable outcome. When OHCA occurred at school (8/44, 18.2%), the outcome was better; seven subjects received bystander CPR and six showed a favorable outcome.

Predictive factors for a favorable outcome after OHCA in pediatric patients

Univariate logistic regression analysis showed that a higher age group, the presence of underlying disease, being at school, the presence of bystander CPR, and shockable AED were significant predictive factors for a favorable outcome (Table 3), whereas OHCA at home lowered the possibility of a favorable outcome. Multiple logistic regression analysis showed that the presence of bystander CPR and OHCA at school were independently predictive for a neurologically favorable outcome. There was no significant interaction between the presence of bystander CPR and OHCA at school or between the presence of bystander CPR and OHCA at home (Table S1).

Discussion

The present study showed that the outcome of pediatric OHCA was associated with age, pre-existing conditions, prior activity, location, and bystander CPR. These factors overlapped with each other. Three major pre-existing conditions of OHCA were CV disease, psychiatric/behavioral diseases, and neurological / neuromuscular disease. Finally, multivariate logistic regression analysis showed that the presence of bystander CPR and occurrence of OHCA at school were independently predictive of a favorable neurological outcome in pediatric OHCA.

Subjects with CV disease as pre-existing conditions showed a high rate of favorable neurological outcomes among subjects with pre-existing conditions. One of the possible reasons why CV disease was the most common among pre-existing conditions, and the reason why the outcome of subjects with CV disease was better than others is the presence of a nationwide school-based CV screening program in Japan.[14,15] Awareness of underlying CV disease may encourage school staff or peers to start early bystander CPR.[5,6] Consequently, a screening program is effective for early diagnosis of some arrhythmia syndromes and prevention of symptoms.[14,15] On the other hand, the present study also showed that the outcome of OHCA of subjects with CV disease was different between subjects with arrhythmias and those with cardiomyopathy/myocarditis. Cardiomyopathy, particularly hypertrophic cardiomyopathy, is still one of the major causes of OHCA with a poor outcome or sudden death in the young in the present and previous studies,[16,17] suggesting that new strategies are required for children and adolescents with hypertrophic cardiomyopathy to prevent OHCA.

Multivariate analysis in the present study showed that the presence of bystander CPR and occurrence of OHCA at school were independently predictive of a favorable outcome. The presence of bystander CPR as a predictive factor of a favorable outcome is consistent with previous studies.[2,4,11] In Japan, deployment of AED in schools has been strongly advocated since implementation of a nationwide public access defibrillation program in 2004.[5,12] At least one AED has been implemented in more than 99% of all elementary, junior high, and

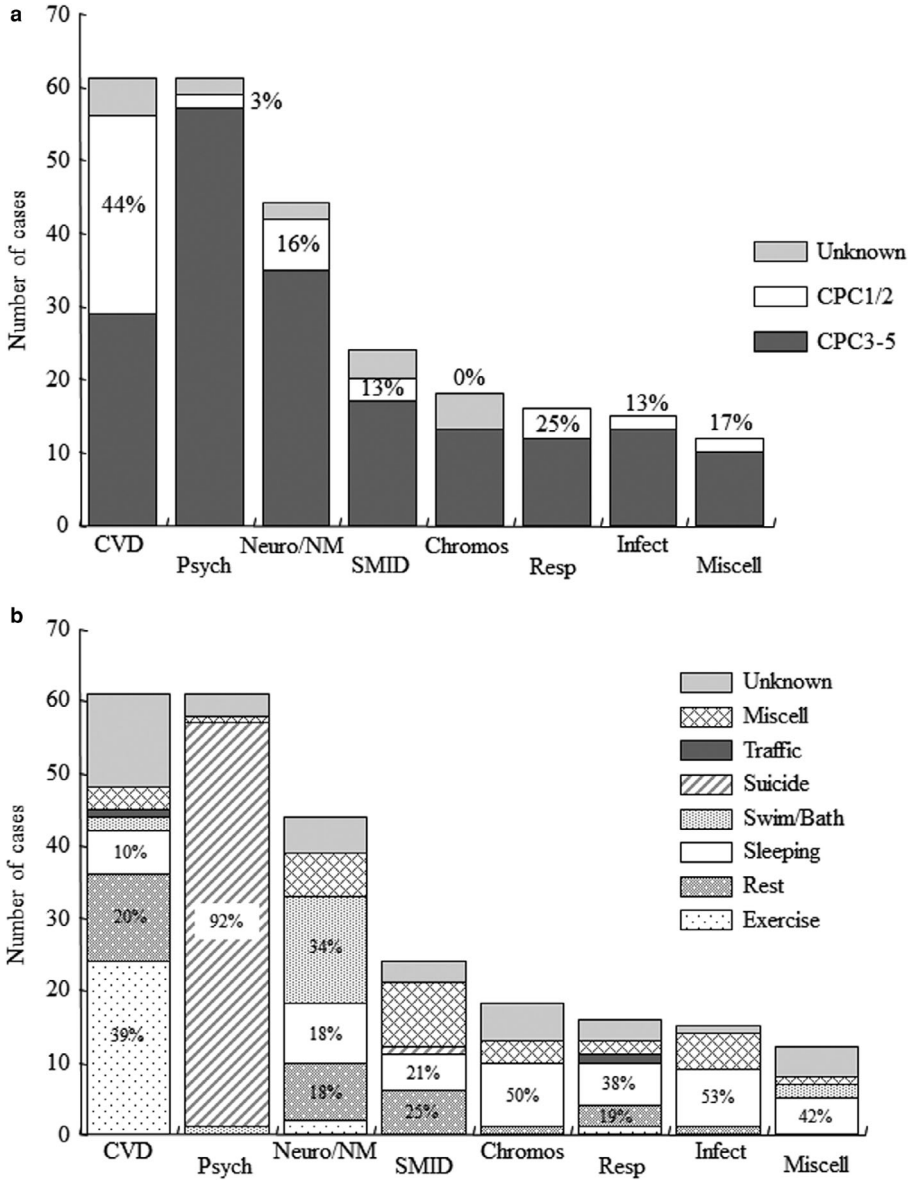

Fig. 5 Outcome by pre-existing conditions (a) and prior activity in each underlying disease (b). Numerals depict percentages of CPC1/2 (a) and prior activity (b) in each underlying disease. Abbreviations; CVD, cardiovascular disease; neuro/NM, neurological/neuromuscular disease; SMID, severe motor and intellectual disability; chromo., chromosomal aberrations or malformation syndrome; resp., respiratory disease; Infec, infectious disease.

high schools in Japan.[18] Widespread inclusion of AEDs in school might promote understanding of importance of bystander CPR and use of AEDs. Recent reports in adults also showed that, in exercise-related OHCA, an increase in bystander CPR and AED use were associated with a favorable neurological outcome.[19,20]

The present study revealed that neurological / neuromuscular disease ranked third in pre-existing conditions of pediatric OHCA and the prevalent prior activity was swimming/bathing. Additionally, 13 of 21 OHCA cases with epilepsy occurred during bathing (n = 11) or swimming (n = 2). Among sudden unexpected death in epilepsy,[21,22] bathtub-related drowning in adults[23] and non-bathtub-related drowning in pediatric cases[24,25] are prevalent causes of drowning. The relative risk of drowning in pediatric patients with epilepsy was 2.4 to 5.8 times higher than that in the total population in Australia.[25] One of the reasons for a higher incidence of bathtub-related drowning in the present study than in other pediatric series

Table 3 Predictive factors for a neurologically favorable prognosis in infants and preschool children by logistic regression analysis (N=555)

Variables	Reference	Univariate Regression				Multivariate Regression			
		n	Odds	95%CI	*P* value	n	Odds	95%CI	*P* value
Age	Per age groups[†]	555	1.54	1.28–1.86	<0.001	518	0.99	0.67–1.47	0.97
Sex (male[‡])	Female	555	0.80	0.51–1.27	0.35				
Pre-existing conditions	Not present	555	1.38	0.87–2.13	0.16				
Pre-existing conditions[§]	Miscellaneous	233	1.52	0.50–4.62	0.46				
Prior activities	Unknown	555	2.24	0.99–5.05	0.05				
Prior activities[¶]	Rest[††]	480	0.22	0.11–0.44	<0.001				
At school	Not at school	555	31.0	15.1–63.8	<0.001	518	6.83	2.33–20.1	<0.001
At school[‡‡]	Outside school/home[‡‡]	189	12.6	5.77–27.3	<0.001				
At home	Not at home	555	0.12	0.07–0.19	<0.001	518	0.62	0.27–1.39	0.24
At home[§§]	Outside school/home[§§]	502	0.24	0.14–0.43	<0.001				
Witnessed	Not witnessed	521	42.0	20.3–87.0	<0.001	518	2.24	0.85–5.85	0.10
BS-CPR	Absence of BS-CPR	529	284.3	68.3–1184	<0.001	518	119.4	25.6–556.3	<0.001
AED shockable	AED not shockable	553	7.72	4.28–13.9	<0.001	518	0.60	0.24–1.50	0.60

[†]Age groups were assigned as 0 for 0 years old, 1 for 1–5 years old, 2 for 6–11 years old, and 3 for 12–19 years old. ‡Boys were assigned as 1 and girls were assigned as 2. §This "Pre-existing condition" includes all subjects with pre-existing conditions except for the miscellaneous group (reference group). ¶Prior activities include all subjects with known prior activities without rest (reference group). ††Prior activity (reference was rest), ‡‡At school (reference was outside school/home), and §§At home (reference was outside school/home) were used as dependent variables in univariate analyses, and the variable were significant; however, they were not used in the multivariate regression analysis because a total number of cases that were available in the multivariate analysis decreased. A neurologically favorable outcome was assigned as 1 and an unfavorable outcome was assigned as 0. AED, automated external defibrillator; BS-CPR, bystander-initiated cardiopulmonary resuscitation; 95% CI, confidence interval; CVD, cardiovascular disease; odds, odds ratio.

might be a higher median age (16 years). These data indicate that we should inform patients, parents, and school staff about the possibility of drowning during bathing and swimming, and about measures to prevent drowning.

Out-of-hospital cardiac arrest out-of-hospital cardiac arrest is most prevalent in infants among pediatric OHCA[8,10] and the most prevalent situation was during sleeping in the present study. After an initial decrease in the overall sleep-related infant death rate in the 1990s, it has not declined in more recent years.[25] Consequently, sleep-related sudden death in infants is still a major concern worldwide. We should reinforce new recommendations for a safe infant sleeping environment[26] and further progress in medicine during sleep in infancy is required.

Suicide and accidents were also major causes of OHCA, particularly in adolescent. Suicide accounted for 24.2% and accidents did for 15.8% of adolescent OHCA in the present study. Both are important and difficult issues to solve; however, we should also make an effort to protect children and adolescents from these issues.

There are limitations in the present study. First, we discussed known pre-existing disease / health conditions; however, the present study did not mean that the pre-existing condition was the exact cause of OHCA, but the study showed that the prevalence or outcome of pediatric OHCA is associated with the pre-existing condition. Conversely, there might be many more cases with pre-existing disease/health conditions that were not reported in the answer to the questionnaires. Second, we did not include information on the initial documented rhythm, presence or absence of dispatcher CPR instructions, and CPR maneuvers (chest compression only or not), which are directly associated with outcome in infants and children. This information should be obtained because our findings might be clarified through these findings. Third, the percentage of neurologically favorable outcomes in the present study (Fig. 2) was slightly higher (not significant) than that in all cases that occurred in Kyushu area (Fig. S1) in 6–11 and 12–19 age groups. There may have been a trend for reporting OHCA cases with a neurologically favorable outcome from local fire departments, school boards, or school doctors in the present study. Fourth, our data did not contain data from emergency hospitals because the questionnaires were sent to local fire departments, school doctors, and school boards.

In conclusion, the rate and outcome of pediatric OHCA is based on age, pre-existing conditions, particularly CV disease and neurological/neuromuscular disease, prior activity, location, and the presence of bystander CPR. These factors overlap with each other. These findings might be useful for preventing and improving the outcome of pediatric OHCA.

Acknowledgments

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Disclosure

The authors declare no conflict of interest.

Author contributions

All authors contributed to the study conception and design; All authors performed material preparation and data collection; M.Y. performed statistical analysis and wrote the first draft of the manuscript; All authors read and approved the final manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Fig. S1. Actual pediatric OHCA cases for each age group from 2012–2016 in Japan from the Fire and Disaster Management Agency (FDMA) of Japan. Numerals depict percentages of a neurologically favorable outcome (CPC1/2) in each age groups (b). The rate of a favorable outcome in the age groups of 12–19 years in the present study (Fig. 2) was significantly higher than that shown by FDMA data ($P = 0.01$) (Supporting Figure) by Fisher's exact probability test. Abbreviations: CPC1/2, cerebral performance categories 1 or 2; CPC3-5, cerebral performance categories 3 to 5.

Table S1. Predictive factors for a neurologically favorable prognosis in multivariate regression models with interaction arms. a. {at school & BS-CPR (+)} and {at home & BS-CPR (+)} as the interaction term. b. {at school & BS-CPR (+)} as the interaction term. c. {at home & BS-CPR (+)} as the interaction term. Abbreviations: AED, automated external defibrillator; BS-CPR (+), presence of bystander-initiated cardiopulmonary resuscitation; BS-CPR (−), absence of BS-CPR; CI, confidence interval; odds, odds ratio. A neurologically favorable outcome was assigned as 1 and an unfavorable outcome was assigned as 0. aAge groups were assigned as 0 for 0 years old, 1 for 1-5 years old, 2 for 6–1 years old, and 3 for 12–19 years old.

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ORIGINAL ARTICLE
Cardiomyopathy

Electrocardiographic Diagnosis of Hypertrophic Cardiomyopathy in the Pre- and Post-Diagnostic Phases in Children and Adolescents

Masao Yoshinaga, MD, PhD; Hitoshi Horigome, MD, PhD; Mamoru Ayusawa, MD, PhD; Kazushi Yasuda, MD; Shigetoyo Kogaki, MD; Shozaburo Doi, MD, PhD; Sigeru Tateno, MD, PhD; Kunio Ohta, MD, PhD; Tatsunori Hokosaki, MD, PhD; Eiki Nishihara, MD; Mari Iwamoto, MD, PhD; Naokata Sumitomo, MD, PhD; Hiroya Ushinohama, MD, PhD; Naomi Izumida, MD, PhD; Nobuo Tauchi, MD, PhD; Yoshiaki Kato, MD, PhD; Taichi Kato, MD, PhD; Toshiyuki Chisaka, MD, PhD; Takashi Higaki, MD, PhD; Tatsuya Yoneyama; Katsumi Abe, MD; Yoshihiro Nozaki, MD, PhD; Akiko Komori, MD; Satoru Kawai, MD; Yumiko Ninomiya, MD; Yuji Tanaka, MD, PhD; Norihito Nuruki, MD; Masahiro Sonoda, MD, PhD; Kentaro Ueno, MD, PhD; Daisuke Hazeki, MD, PhD; Yuichi Nomura, MD, PhD; Seiichi Sato, MD, PhD; Keiichi Hirono, MD, PhD; Susumu Hosokawa, MD, PhD; Fumie Takechi, MD; Yuichi Ishikawa, MD, PhD; Tadayoshi Hata, MD, PhD; Fukiko Ichida, MD, PhD; Seiko Ohno, MD, PhD; Naomasa Makita, MD, PhD; Minoru Horie, MD, PhD; Shouji Matsushima, MD, PhD; Hiroyuki Tsutsui, MD, PhD; Hiromitsu Ogata, PhD; Hideto Takahashi, PhD; Masami Nagashima, MD, PhD

Background: The usefulness of electrocardiographic (ECG) voltage criteria for diagnosing hypertrophic cardiomyopathy (HCM) in pediatric patients is poorly defined.

Methods and Results: ECGs at the 1st grade (mean [±SD] age 6.6±0.3 years) were available for 11 patients diagnosed with HCM at around the 7th grade (13.2±0.3 years). ECGs were available for another 64 patients diagnosed with HCM in the 1st (n=15), 7th (n=32), and 10th (n=17) grades. Fifty-one voltage criteria were developed by grade and sex using 62,841 ECGs from the general population. Voltage criteria were set at the 99.95th percentile (1/2,000) point based on the estimated prevalence of childhood HCM (2.9 per 100,000 [1/34,483]) to decrease false negatives. Conventional criteria were from guidelines for school-aged children in Japan. Of 11 patients before diagnosis, 2 satisfied conventional criteria in 1st grade; 5 (56%) of the remaining 9 patients fulfilled 2 voltage criteria (R wave in limb-lead I [RI]+S wave in lead V3 [SV3] and R wave in lead V3 [RV3]+SV3). Robustness analysis for sensitivity showed RV3+SV3 was superior to RI+SV3. For all patients after diagnosis, RI+SV4 was the main candidate. However, conventional criteria were more useful than voltage criteria.

Conclusions: Early HCM prediction was possible using RV3+SV3 in >50% of patients in 1st grade. Voltage criteria may help diagnose prediagnostic or early HCM, and prevent tragic accidents, although further prospective studies are required.

Key Words: Children; Diagnosis; Electrocardiography; Hypertrophic cardiomyopathy; Prevention

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Department of Pediatrics (M.Y., Y. Ninomiya, Y.T.), Department of Cardiovascular Medicine (N.N., M.S.), National Hospital Organization Kagoshima Medical Center, Kagoshima; Department of Child Health, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba (H.H.); Department of Pediatrics, Nihon University Itabashi Hospital, Tokyo (M.A.); Department of Pediatric Cardiology, Kids' Heart Center, Aichi Children's Health and Medical Center, Obu (K.Y., S. Kawai); Department of Pediatrics and Neonatology, Osaka General Medical Center, Osaka (S. Kogaki); Department of Pediatrics, National Hospital Organization Disaster Medical Center, Tokyo (S.D.); Department of Pediatrics, Chiba Kaihin Municipal Hospital, Chiba (S.T.); Department of Pediatrics, Kanazawa University, Kanazawa (K.O.); Department of Pediatrics, Yokohama City University Hospital, Yokohama (T. Hokosaki); Pediatric Cardiology, Ogaki Municipal Hospital, Ogaki (E.N.); Children's Center, Saiseikai Yokohamashi Tobu Hospital, Yokohama (M.I.); Department of Pediatric Cardiology, Saitama Medical University International Medical Center, Hidaka (N.S.); Pediatric Cardiology, Ohori Children's Clinic, Fukuoka (H.U.); Pediatric Cardiology, Akebonocho Clinic, Tokyo (N.I.); Aichi Saiseikai Rehabilitation Hospital, Nagoya (N.T., M.N.); Department of Pediatric Cardiology (Y.K.),
(Footnote continued the next page.)

Hypertrophic cardiomyopathy (HCM) remains one of the major causes of sudden cardiac death (SCD) or aborted cardiac arrest (ACA) in youth.[1-5] Electrocardiographic (ECG) findings overlap between HCM and athletes.[6] Current recommendations for ECG interpretation are based on asymptomatic athletes aged 12–35 years.[7] In contrast, the median age of patients with childhood-onset HCM was reported to be 12.2 years.[3] A recommendation for ECG interpretation is required for asymptomatic children because many potential competitive or professional athletes may start sports activities before these ages. Early diagnosis and early intervention, such as lifestyle modification or the introduction of medications, may prevent children and adolescents from competitive sports-related SCD or ACA.

A standard 12-lead ECG in HCM patients shows a variable combination of left ventricular hypertrophy (LVH), ST and T wave abnormalities, and pathological Q waves.[1] Of these, voltage criteria have been reported for LVH screening.[8-15] However, despite interventricular hypertrophy being a characteristic feature of HCM, few studies have investigated whether single R or S waves or a combination of R and S waves can be used to detect interventricular hypertrophy in pediatric HCM patients.[16]

A nationwide, school-based ECG screening program for heart diseases in the 1st, 7th, and 10th graders (aged 6, 12 and 15 years, respectively) in Japan was set by law in 1994;[17] the program is also been performed in 4th graders in some regions. As part of this screening program in Japan , HCM is most frequently diagnosed around the 7th grade.[18] A previous study showed that approximately 60% (27/44) of school-aged children and adolescents who experienced SDS or ACA were not diagnosed with HCM before their cardiac events,[19] suggesting that the current screening system may not be effective for the early diagnosis of HCM and may not allow for interventions before the appearance of symptoms.[18] When participants are diagnosed with HCM at the 7th grade screening or later, the 1st grade ECGs are available for review in some areas in Japan where the ECGs of participants are digitally stored.[20]

The aim of the present study was to determine whether voltage criteria could be used to predict a potential diagnosis of HCM at the 1st grade screening in patients who were diagnosed at the 7th grade or later screening (i.e., approximately 6 years before the actual HCM diagnosis). Furthermore, we examined the utility of voltage criteria and conventional criteria for diagnosing HCM patients who were diagnosed at the 1st, 7th, and 10th grade screening.

Methods

Subjects

In all, 124 patients with HCM who visited 1 of 14 hospitals in Japan from 2000 to 2019 and who were <20 years old at their first visit were included in this study. Of 202 ECGs from 124 patients, 44 ECGs from 24 patients with secondary HCM and 37 ECGs from 24 patients with findings that affect the QRS voltages (i.e., complete bundle branch block) were excluded (**Figure 1**). Patients were divided into pre- and post-diagnostic groups.

This study was approved by the Ethics Committee of the National Hospital Organization Kagoshima Medical Center (27-9 and 27-28).

Prediagnostic Group

The prediagnostic group included 11 patients (9 boys, 2 girls) who visited the National Hospital Organization Kagoshima Medical Center and were diagnosed with HCM at a mean (±SD) age of 13.2±2.0 years and whose ECGs at the 1st grade screening program were retrospectively available (**Table 1**). The mean (±SD) interval between the 1st grade ECG recordings and actual diagnosis was 6.4±1.8 years. A diagnosis of HCM was made when the left ventricular (LV) wall thickness was ≥15 mm; this is a robust diagnostic criterion for adults in this group.[1] Two patients with LV wall thickness <15 mm were pathologically diagnosed by myocardial biopsy (Cases 10 and 11).[9]

The genetic background in this group was determined using the ClearSeq Halo HS cardiomyopathy panel (Agilent Technologies, Santa Clara, CA, USA), which included 34 genes, and using a bench top-type next-generation sequencing machine (MiSeq; Illumina, San Diego, CA, USA). Data were analyzed using SureCall software (Agilent Technologies). Detected variants were confirmed using the Sanger method and variants classified as pathogenic or likely pathogenic in ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) were judged as pathogenic mutations.

Post-Diagnostic Group

The post-diagnostic group included 64 patients who were

Omics Research Center (N.M.), National Cerebral and Cardiovascular Center, Suita; Department of Pediatrics/Developmental Pediatrics, Nagoya University Graduate School of Medicine, Nagoya (T.K.); Pediatric Cardiology (T.C.), Department of Regional Pediatrics and Perinatology (T. Higaki), Ehime University Graduate School of Medicine, Toon; Fukuda Denshi Co., Ltd., Tokyo (T.Y.); Tokyo Health Service Association, Tokyo (K.A.); Department of Pediatrics, University of Tsukuba Hospital, Tsukuba (Y. Nozaki); Department of Pediatrics and Child Health, Nihon University School of Medicine, Tokyo (A.K.); Department of Pediatrics, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima (K.U.); Department of Pediatrics, Kagoshima City Hospital, Kagoshima (D.H., Y. Nomura); Department of Pediatric Cardiology, Okinawa Prefectural Nanbu Medical Center and Children's Medical Center, Okinawa (S.S.); Department of Pediatrics, Faculty of Medicine, University of Toyama, Toyama (K.H.); Department of Pediatrics, Perinatal and Maternal Medicine, Tokyo Medical and Dental University, Tokyo (S.H.); Department of Pediatrics, Chiba Cardiovascular Center, Chiba (F.T.); Department of the Cardiovascular System, Fukuoka Children's Hospital, Fukuoka (Y.I.); Department of Pediatrics, Fujita Health University School of Medicine, Toyoake (T. Hata); Department of Pediatrics, Sanno Hospital, Tokyo (F.I.); Department of Bioscience and Genetics, National Cerebral and Cardiovascular Center Research Institute, Suita (S.O.); Center for Epidemiologic Research in Asia, Shiga University of Medical Science, Otsu (M.H.); Department of Cardiovascular Medicine, Faculty of Medical Sciences, Kyushu University, Fukuoka (S.M., H. Tsutsui); Graduate School of Kagawa Nutrition University, Sakado (H.O.); and Research Managing Director, National Institute of Public Health, Wako (H. Takahashi), Japan

Mailing address: Masao Yoshinaga, MD, PhD, Department of Pediatrics, National Hospital Organization Kagoshima Medical Center, 8-1 Shiroyama-cho, Kagoshima 892-0853, Japan. E-mail: yoshinaga.masao.ks@mail.hosp.go.jp

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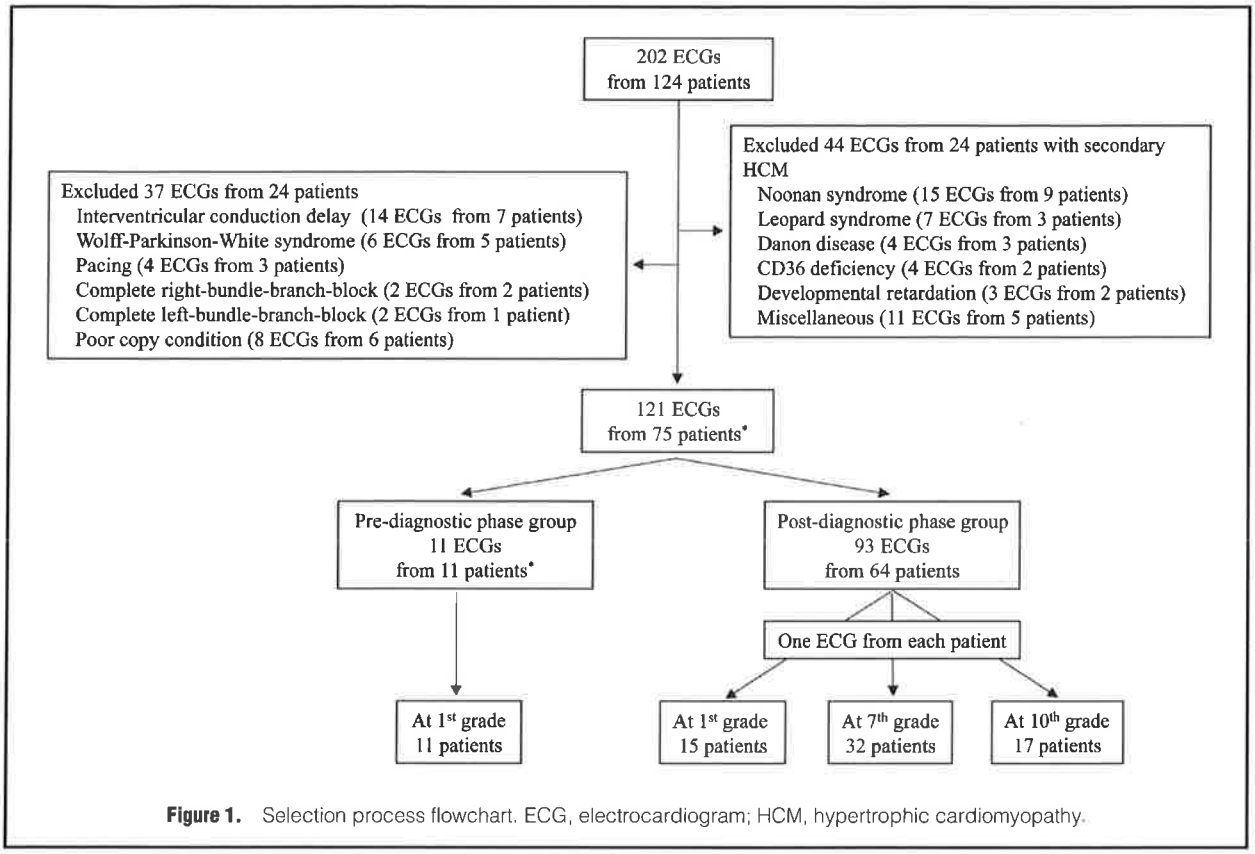

Figure 1. Selection process flowchart. ECG, electrocardiogram; HCM, hypertrophic cardiomyopathy.

already diagnosed with HCM in 1 of 14 hospitals (mean [±SD] 11.2±3.9 years; **Table 2**). ECGs were obtained in the 1st, 7th, and 10th grades, and the earliest ECGs from each patient were used (**Figure 1**). A diagnosis of HCM was made using the 2014 European Society of Cardiology (ESC) guidelines[1] as follows: wall thickness ≥15 mm or z-score >2, where the z-score is defined as the number of standard deviations from the population mean in this group. Genetic tests were not mandatory in this group.

Tentative ECG Screening Criteria

Estimated Prevalence of Pediatric HCM The true prevalence of HCM in childhood is unknown. The annual occurrence of new cases of childhood HCM ranges from 0.24 to 0.47 per 100,000.[21–24] The mean annual occurrence of new cases of childhood HCM (aged <20 years) between 2015 and 2019 in Japan was 0.36 per 100,000 (95% confidence interval [CI] 0.25–0.45 per 100,000),[25] which corresponds with previous reports.[21–24] For example, Arola et al reported a mean annual occurrence of HCM between 1980 and 1991 of 0.24 per 100,000 (95% CI 0.17–0.33 per 100,000) and a prevalence of HCM at the end of 1991 of 2.9 per 100,000 (95% CI 2.0–4.0 per 100,000).[21] Thus, the prevalence of childhood HCM in Japan may be slightly higher than that reported.[21] To decrease the number of false-negative results, a screening rate between 1/2,000 or 1/5,000 may be acceptable. In the present study, we used a screening rate of 1/2,000 (99.95th percentile point) of the reference population.

Reference ECGs to Establish Screening Criteria for Increased R/S Wave Voltages To establish the screening voltage criteria, ECGs of 1st, 7th, and 10th graders among the general population who participated in screening programs were obtained.[26] ECGs were recorded at school at a speed of 25 mm/s and a sampling rate of 500 Hz using a portable PC-based system (Fukuda Denshi, Tokyo, Japan). In the Japanese screening programs, where numerous ECGs of children are recorded at the same time, narrow bandwidth filters (0.5–35 Hz) were occasionally used to remove noise. Thus, we prepared 2 ECG reference values for a narrow bandwidth and a routine bandwidth (0.05–150 Hz), as detailed below.

Reference ECGs for the Narrow Bandwidth The process used to develop the ECG reference values was previously reported.[26] Briefly, 56,753 digitally stored ECGs of participants in a school-based ECG screening system in Kagoshima, Japan, were obtained. Each ECG was manually reviewed by 2 pediatric cardiologists, and only ECGs with sinus rhythm were included. ECGs of subjects with arrhythmias, ST/T changes, or inappropriate recordings were excluded. Finally, 48,401 ECGs from 16,773 1st graders (8,350 boys, 8,423 girls), 18,126 7th graders (8,943 boys, 9,183 girls), and 13,502 10th graders (6,477 boys, 7,025 girls) were selected.[26]

Reference Values for the Routine Bandwidth In all, 29,605 ECGs were recorded at the schools using a portable PC-based system (Fukuda Denshi) in Kagoshima, Ehime, Kanagawa, and Tokyo in 2016 and 2017. After reviewing the ECGs using the same process as for the narrow bandwidth ECGs, a final number of 14,400 ECGs from 2,994 1st graders (1,611 boys, 1,383 girls), 3,646 7th graders (1,634 boys, 2,012 girls), and 7,758 10th graders (4,019 boys, 3,739 girls) were selected.

Table 1. Characteristics of Subjects in the Prediagnostic Group

Case no.	Sex	Age at Dx	Dx events	IVSTh[d] at Dx (mm)	PWTh[d] at Dx (mm)	Type of HCM[e]	Age at 1st ECG	Interval[a] (years)	Prognosis	Genes	Variants
1	M	11.9	Screening	20.8	11.1	ASH	6.6	5.3	Alive	Not identified	
2	M	12.3	Screening	27.0	10.2	ASH	6.2	6.0	Sudden death	Not done	
3	M	13.1	Screening	16.4	13.1	Diffuse	7.0	6.0	Alive	Not done	
4	F	16.0	Screening	17.1	11.0	ASH	6.9	9.1	Alive	*MYH7*	c.3158G>A, p.R1053Q, rs587782962
5[b]	F	9.6	Screening	17.2	6.1	Apical[f]	6.3	3.3	Alive	*MYH7*	c.1357C>T, p.R453C, rs121913625
6[b]	M	13.0	Familial study	18.3	13.1	ASH	6.8	6.2	Alive	*MYH7*	c.1357C>T, p.R453C, rs121913625
7	M	12.6	Screening	15.2	12.0	Diffuse	6.4	6.2	Alive	*MYBPC3*	c.1484G>A, p.R495Q, rs200411226
8	M	12.3	Screening	27.5	9.3	ASH	6.2	6.0	Alive	Not identified	
9	M	12.9	Screening	18.7	8.8	ASH	6.9	6.0	ACA	*MYH7*	c.2155C>T, p.R719W, rs121913637
10[c]	M	15.6	Screening	11.9	11.9	Diffuse	6.7	8.9	Alive	Not identified	
11[c]	M	16.3	OHCA	14.0	10.0	ASH	6.5	9.9	ACA	*TNNT2*	c.418C>T, p.R140C, homozygous, rs397516463
Mean±SD		13.2±2.0		18.6±4.9	10.6±2.1		6.6±0.3	6.4±1.8			

[a]Interval between the age at the time of electrocardiography (ECG) in 1st grade and the age at diagnosis. [b]Cases 5 and 6 were members of the same family. [c]Cases 10 and 11 were diagnosed pathologically. [d]Measurements of the left ventricular wall were made at the maximum point of the interventricular septum or the posterior wall. [e]Asymmetric septal hypertrophy was defined as a ratio of the septum to posterior wall thickness ≥1.3 according to the traditional definition,[33] whereas diffuse-type septal hypertrophy was defined as a ratio <1.3. [f]Case 5 showed hypertrophy of the apical region (apical hypertrophy type) that extended to the distal portion of the interventricular septum and lateral portion of the left ventricle. ACA, aborted cardiac arrest; Apical, apical hypertrophy; ASH, asymmetric septal hypertrophy; Dx, diagnosis or diagnostic; F, female; IVSTh, interventricular septum thickness (in mm); M, male; *MYBP3*, myosin binding protein C; *MYH7*, β-myosin heavy chain; OHCA, out-of-hospital cardiac arrest; PWTh, posterior wall thickness (in mm); *TNNT2*, troponin T.

Screening Criteria for Increased R/S Wave Voltages The following 51 voltage criteria were assessed as screening criteria for screening HCM patients at 1/2,000 point in the general population:

1. R/S waves of each single lead
   - An R wave of each of the 12 leads (the voltages of the R and R' waves were summed if present)
   - An S wave of each of the 12 leads
2. A combination of R/S waves of different leads that have already been published
   - Cornell criteria: R wave in lead aVL (RaVL)+S wave in lead V3 (SV3) [RaVL+SV3][8] (Criterion A)
   - Pediatric-specific criteria (RaVL+SV2)[9]
   - Gubner-Ungerleider criteria: R wave in lead I (RI)+S wave in lead III (SIII) [RI+SIII][10]
   - Lewis criteria: RI+SIII−(R wave in lead III [RIII]+S wave in lead I [SI]) [RIII+SI][11]
   - Sokolow-Lyon criteria: SV1+RV5 and SV1+RV6[12]
   - The deepest S wave in any lead (S_D) and the S wave in lead V4 (S_D+SV4)[13] (Criterion B)
   - RI+SV4[14] (Criterion C)

RaVL+SV4, S_D+SV3, RI+S2, and RI+SV3 were included to compare Criteria of A, B, and C. Approximately 80% of the reference population showed the deepest S wave in lead V2. Thus, S_D+SV2 was not investigated. In addition, the total 12-lead QRS voltage[15] was not investigated in the present study because it is difficult to use in the clinical setting.

3. A combination of an R wave in lead V1 (RV1) and S waves in the mid-precordial leads: RV1+SV2, RV1+SV3, and RV1+SV4

In one case in the prediagnostic group, high voltage R waves in lead V1 and relatively deep S waves in the precordial leads were seen. Thus, a combination of RV1 and S waves in the precordial leads was included.

4. A combination of R/S waves in the mid-precordial leads:
   - RV2+SV2, RV2+SV3, and RV2+SV4
   - RV3+SV2, RV3+SV3, and RV3+SV4
   - RV4+SV2, RV4+SV3, and RV4+SV4
5. A combination of S waves of different mid-precordial leads: SV2+SV3, SV2+SV4, and SV3+SV4.

Screening Criteria for Cardiovascular Disease in the School-Based Screening Program in Japan

Screening criteria in the school-based screening program in Japan are available in published form[27] and on through the Japanese Circulation Society website[28] and include

Table 2. Characteristics of the Post-Diagnostic Groups

	1st grade (n=15)	7th grade (n=32)	10th grade (n=17)
No. males/females	7/8	19/13	9/8
Age at ECG[a] (years)	6.7±0.6	12.9±0.6	15.8±0.7
Age at diagnosis (years)	5.2±2.4	12.1±1.6	14.6±1.6
Interval[b] (years)	1.5±2.3	0.9±1.3	1.2±1.9
Diagnostic events			
At screening	5 (33)	25 (78)	9 (53)
Through symptoms	0	1 (3)	3 (18)
Familial study	4 (27)	1 (3)	0
By chance	6 (40)	4 (13)	1 (6)
Unknown	0	1 (3)	3 (18)
Age at echocardiography[c] (years)	6.7±0.5 (n=10)	13.0±0.8 (n=23)	16.3±2.5 (n=11)
IVSTh (mm)	16.1±5.7	16.0±6.6	17.0±5.5
PWTh (mm)	7.6±1.3	11.4±4.7	13.4±5.3
Prognosis			
Alive	15 (100)	26 (81)	14 (82)
OHCA	0	3 (9)	1[d] (6)
Transplantation	0	1 (3)	0
Death	0	1 (3)	1[d] (6)
Unknown	0	1 (3)	2 (12)

Unless indicated otherwise, data are given as the mean±SD or n (%). [a]Age at which electrocardiograms (ECG) used in this study were recorded. [b]Interval between the age at diagnosis and the age at the time of ECG recording. [c]Age at which echocardiography was performed in the 1st, 7th, or 10th grades. [d]The same patient. IVSTh, interventricular septum thickness; OHCA, out-of-hospital cardiac arrest; PWTh, posterior wall thickness.

HCM-related findings (abnormal Q waves, ST depression, and T wave inversion), right ventricular hypertrophy, and LVH. The "conventional criteria" used in the present study are those included in these guidelines. In the present study, an ECG was considered abnormal if the patient fulfilled one of the criteria of "Group A" in those guidelines.[27,28]

Additional Criteria for Pathological Q Waves

The deepest Q wave of leads III and V6 was less than −0.7 mV in all 3 (1st, 7th, and 10th) grades in the general population for both the narrow and routine bandwidth groups. We defined a deep Q wave greater than −0.7 mV as an abnormal Q wave.

Statistical Analysis

All data are presented as the mean±SD. Statistical analyses were performed using IBM® SPSS® Statistics v23.0 (IBM Japan, Tokyo, Japan). Tentative criteria for increased R/S voltages at the 99.95th percentile (1/2,000) point were calculated by grade and sex. To estimate the 99.95th percentile (1/2,000) point, the bundled PERCENYILE.EXC function in EXEL 2016® (Microsoft Japan, Tokyo, Japan) was used if the size of a group exceeded 2,000, where the percentile of the maximum value exceeds the 99.95th percentile (2,000/2,001=0.99950025>0.9995). When the size of a group, n, was <2,000 (e.g., n=1,611), the 99.95th percentile x was estimated by extrapolation using the following formula:

$$x = \frac{(p_{nth} - 0.9995)x_{n-1th} + (0.9995 - p_{n-1th})x_{nth}}{(p_{nth} - p_{n-1th})}$$

where p_{nth}=n/(n+1)=1,611/1,612 (0.99938), p_{n-1th}=(n−1)/(n+1)=1,610/1,612 (0.99875), and x_{nth} and x_{n-1th} are the largest and the second largest values of the group of size n, respectively.

When the sensitivity at the 99.95th percentile (1/2,000) screening point was the same between several voltage criteria, the robustness of the sensitivity of each voltage criterion was determined using additional 1/1,500 and 1/2,500 screening points. The sensitivity of a criterion was considered to be more robust than others when the square of the distance to the ideal sensitivity and specificity (i.e., [1−sensitivity]^2+[1−specificity]^2) was unchanged.

Results

Tentative Screening Criteria for Increased R/S Voltage Criteria in Each Lead

Tentative criteria for the increased R/S voltages at the 99.95th percentile (1/2,000) point for the narrow and routine bands are shown in **Supplementary Table 1A** and **1B**, respectively.

Patients Fulfilling the Increased Voltage Criteria

First Graders of the Prediagnostic Group For the 11 patients in the 1st grade in the prediagnostic group, the highest sensitivity (45%) was found for the screening criteria of RI+SV3, RV2+SV3, and RV3+SV3; all these criteria included the S wave voltage in lead V3 (**Supplementary Table 2**). Two of these 11 patients were screened using the conventional criteria during the 1st grade screening program (QS pattern [Case 10] and right ventricular hypertrophy [Case 11]). However, they were diagnosed as normal because they did not have an increased ventricular wall thickness or congenital heart diseases on echocardiography.[20]

The ECGs of all 11 patients are shown in **Supplementary Figure 1**. The remaining 9 patients who showed a promi-

nent LV wall thickness that fulfilled the diagnostic criteria for adults at their 7th grade screening did not fulfill conventional criteria at their 1st grade screening. Of these 9 patients, the highest sensitivity (56%) was still found for the screening criteria of RI+SV3 and RV3+SV3. The RV3+SV3 criterion was preferable to the RI+SV3 criterion because robustness analysis showed that the sensitivity, specificity, and deviation from the ideal point of the sensitivity and specificity ([1−sensitivity]^2+[1−specificity]^2) of RV3+SV3 was unchanged (robust), even when the screening point changed from 1/2,000 to 1/1,500 or 1/2,500 (**Table 3**). Thus, the tentative criterion of RV3+SV3 for the early diagnosis of 1st graders in the clinical setting was 6.0 and 5.0 mV in boys and girls, respectively, for the narrow bandwidth group and 6.5 and 6.1 mV in boys and girls, respectively, for the routine bandwidth group (**Supplementary Table 1A,1B**). Nevertheless, these criteria should be further revised after obtaining a larger number of ECGs for the routine bandwidth from the general population.

First Graders of the Post-Diagnostic Group Of the 15 patients in the 1st grade in the post-diagnostic group, the highest sensitivity (60%) was found for SV2+SV4, whereas the criteria with the second-highest (53%) sensitivity were RaVL+SV3, S_D+SV3, RI+SV3, RI+SV4, and SV2+SV3

Table 3. Robustness of Sensitivity of the Voltage Criteria of R Wave in Limb-Lead I (RI)+S Wave in Lead V3 (SV3) and R Wave in Lead V3 (RV3)+SV3 at the 1/1,500, 1/2,000, and 1/2,500 Screening Points

Screening point	RI+SV3			RV3+SV3		
	Sensitivity	Specificity	Value	Sensitivity	Specificity	Value
1/1,500	0.5556	0.9993	0.1975	0.5556	0.9993	0.1975
1/2,000	0.5556	0.9995	0.1975	0.5556	0.9995	0.1975
1/2,500	0.4444	0.9996	0.3087	0.5556	0.9996	0.1975

Value refers to the square of the distance to the ideal sensitivity and specificity (i.e., [1−sensitivity]^2+[1−specificity]^2), with smaller values indicating a better candidate criterion.

Table 4. Number of Patients Who Fulfilled the Criteria and the Sensitivity of All Surrogate Markers in the Pre- and Post-Diagnostic Groups

	Pre-diagnostic phase	Post-diagnostic phase		
	1st grade (n=11)	1st grade (n=15)	7th grade (n=32)	10th grade (n=17)
RI	0 (0)	2 (13)	12 (38)	1 (6)
RII	0 (0)	3 (20)	2 (6)	3 (18)
RIII	0 (0)	1 (7)	1 (3)	3 (18)
RaVR	0 (0)	5 (33)	2 (6)	4 (24)
RaVL	0 (0)	2 (13)	9 (28)	3 (18)
RaVF	0 (0)	1 (7)	1 (3)	3 (18)
RV1	2 (18)	2 (13)	8 (25)	1 (6)
RV2	1 (9)	2 (13)	6 (19)	2 (12)
RV3	0 (0)	1 (7)	1 (3)	2 (12)
RV4	0 (0)	1 (7)	1 (3)	0 (0)
RV5	0 (0)	2 (13)	2 (6)	0 (0)
RV6	0 (0)	1 (7)	2 (6)	0 (0)
SI	0 (0)	3 (20)	3 (9)	2 (12)
SII	0 (0)	3 (20)	1 (3)	4 (24)
SIII	0 (0)	3 (20)	6 (19)	4 (24)
SaVR	0 (0)	3 (20)	5 (16)	2 (12)
SaVL	0 (0)	0 (0)	0 (0)	3 (18)
SaVF	0 (0)	3 (20)	4 (13)	4 (24)
SV1	0 (0)	1 (7)	1 (3)	0 (0)
SV2	2 (18)	4 (27)	1 (3)	1 (6)
SV3	4 (36)	7 (47)	1 (3)	2 (12)
SV4	0 (0)	7 (47)	3 (9)	2 (12)
SV5	1 (9)	5 (33)	4 (13)	3 (18)
SV6	0 (0)	5 (33)	2 (6)	3 (18)
RaVL+SV2	3 (27)	6 (40)	5 (16)	2 (12)
RaVL+SV3	4 (36)	8 (53)	4 (13)	5 (29)
RaVL+SV4	1 (9)	7 (47)	11 (34)	5 (29)
RI+SIII	0 (0)	3 (20)	11 (34)	4 (24)

(**Table 4** continued the next page.)

	Pre-diagnostic phase	Post-diagnostic phase		
	1st grade (n=11)	1st grade (n=15)	7th grade (n=32)	10th grade (n=17)
Lewis	0 (0)	3 (20)	6 (19)	3 (18)
SV1+RV5	0 (0)	2 (13)	3 (9)	0 (0)
SV1+RV6	1 (9)	1 (7)	1 (3)	0 (0)
S_D+SV3	4 (36)	8 (53)	2 (6)	3 (18)
S_D+SV4	4 (36)	7 (47)	2 (6)	2 (12)
RI+SV2	2 (18)	7 (47)	3 (9)	1 (6)
RI+SV3	5 (45)	8 (53)	5 (16)	4 (24)
RI+SV4	1 (9)	8 (53)	14 (44)	6 (35)
RV1+SV2	1 (9)	1 (7)	3 (9)	2 (12)
RV1+SV3	3 (27)	4 (27)	2 (6)	3 (18)
RV1+SV4	3 (27)	7 (47)	11 (34)	3 (18)
RV2+SV2	1 (9)	2 (13)	4 (13)	3 (18)
RV2+SV3	5 (45)	2 (13)	4 (13)	3 (18)
RV2+SV4	2 (18)	6 (40)	9 (28)	4 (24)
RV3+SV2	2 (18)	3 (20)	2 (6)	1 (6)
RV3+SV3	5 (45)	4 (27)	3 (9)	2 (12)
RV3+SV4	1 (9)	5 (33)	6 (19)	3 (18)
RV4+SV2	1 (9)	4 (27)	2 (6)	0 (0)
RV4+SV3	3 (27)	5 (33)	2 (6)	0 (0)
RV4+SV4	1 (9)	6 (40)	7 (22)	1 (6)
SV2+SV3	3 (27)	8 (53)	1 (3)	3 (18)
SV2+SV4	2 (18)	9 (60)	2 (6)	3 (18)
SV3+SV4	4 (36)	7 (47)	3 (9)	2 (12)
HCM-related	1 (9)	9 (60)	27 (84)	13 (76)
Abnormal Q	1 (9)	3 (20)	8 (25)	1 (6)
ST depression	0 (0)	4 (27)	12 (38)	5 (29)
T wave inversion	0 (0)	5 (33)	19 (59)	12 (71)
RVH	1 (9)	1 (7)	2 (6)	1 (6)
Conventional criteria	2 (18)	10 (67)	29 (91)	14 (82)

Data show the number of patients with the sensitivity (%) of each marker given in parentheses. HCM, hypertrophic cardiomyopathy; RVH, right ventricular hypertrophy.

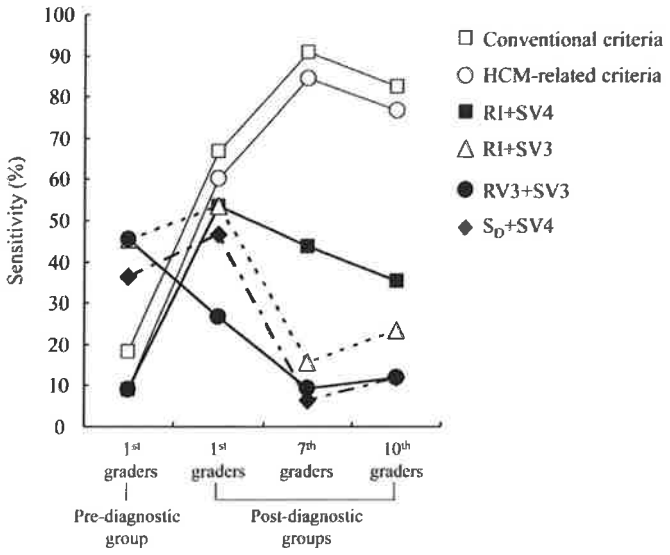

Figure 2. Changes in the sensitivity of the representative criteria. Some voltage criteria showed a higher sensitivity than conventional or hypertrophic cardiomyopathy (HCM)-related criteria in 1st graders in the prediagnostic group. The prediagnostic group included 2 patients who had conventional screening criteria. The RV3+SV3 criterion had a sensitivity of 45% in the prediagnostic group, but failed in the post-diagnostic group. The RI+SV4 criterion showed a low sensitivity in the pre-diagnostic group, but showed a relatively high sensitivity for 1st and 7th graders in the post-diagnostic groups. Conventional and HCM-related criteria showed a low sensitivity for the pre-diagnostic group, but had a higher sensitivity than voltage criteria in the post-diagnostic groups, particularly at the 7th and 10th grades. RI, R wave in limb-lead I; RV3, R wave in lead V3; SV3, S wave in lead V3; S_D, deepest S wave in any lead; SV4, S wave in lead V4.

(**Supplementary Table 3**). In the post-diagnostic group, 10 of 15 patients (67%) met conventional criteria. Of remaining 5 patients who did not meet conventional criteria, 4 were diagnosed by chance (**Supplementary Table 3**). RaVL+SV3, SD+SV3, RI+SV3, RI+SV4, SV2+SV3, and SV2+SV4, which included the S wave voltages in leads V3 or V4 (SV3 or SV4, respectively), had a sensitivity of 60%. These 6 screening criteria had the same sensitivity at 1/1,500 and 1/2,500 (data not shown), suggesting that they are all candidate criteria for screening 1st graders in the post-diagnostic group who do not meet conventional criteria.

Seventh Graders of the Post-Diagnostic Group The highest sensitivity was found for RI+SV4 (44%; **Table 4**). Of the 32 patients in this group, 29 (91%) fulfilled the conventional criteria. Of the 3 remaining patients who did not meet the conventional criteria, 2 fulfilled the voltage criterion of RI+SV4. However, of these 3 patients, 2 showed a flat T wave (and not an inverted T wave as in the conventional criteria) in the left precordial leads and 1 showed a very low voltage R wave in the left precordial leads. Overall, these findings suggest that nearly all 7th graders with HCM may be screened using conventional criteria and abnormal findings.

Tenth Graders of the Post-Diagnostic Group The highest sensitivity was found for RI+SV4, although the sensitivity was low (35%; **Table 4**). Of the 17 patients, 14 (82%) fulfilled the conventional criteria, whereas the remaining 3 patients also had a flat T wave in lead V6, a deep S wave (1.3 mV) in lead V6, and fulfilled the voltage criteria of RV2+SV2 and RV3+SV3.

Candidate Criteria for 1st, 7th, and 10th Graders in the Post-Diagnostic Groups

The sensitivity of representative voltage criteria for the pre- and post-diagnostic groups, including subjects who fulfilled the conventional screening criteria, is shown in **Figure 2**. RI+SV4 was a potential candidate criterion for all post-diagnostic groups because it had one of the highest sensitivities in 1st graders who did not meet conventional criteria, and showed the highest sensitivity in 7th and 10th graders. However, conventional diagnostic criteria were better at diagnosing patients with HCM than the voltage criteria, particularly in the case of 7th and 10th graders (**Figure 2**; **Table 4**). The tentative criterion of RI+SV4 for 1st graders in the clinical setting was 3.2 and 3.0 mV for boys and girls, respectively, and 3.6 mV for both boys and girls with a routine bandwidth (**Supplementary Table 1**). Nevertheless, these criteria should be further revised after obtaining a larger number of ECGs for the routine bandwidth from the general population.

Summary of Sensitivity and Specificity

A summary of the sensitivity of each criterion is presented in **Table 4**. The specificity of each criterion was approximately 99.95% for all screening criteria because the criteria were set to screen 1/2,000 of the general population.

Discussion

The present study showed that early prediction of a potential diagnosis of HCM was possible using the voltage criteria of RI+SV3 and RV3+SV3 in >50% of patients in the 1st grade who were diagnosed in the 7th grade. The robustness of sensitivity data showed that RV3+SV3 was superior to RI+SV3. This strategy may help prevent tragic accidents in patients, although future prospective studies are required. RI+SV4 was also useful for diagnosing patients with HCM in the post-diagnostic groups. The present study showed that the voltage criteria had a lower sensitivity for screening patients with HCM than the conventional criteria for post-diagnostic groups, particularly for 7th and 10th graders.

ECG findings in HCM patients are known to precede echocardiographic findings.[20,29,30] Early diagnosis via ECG may prevent children and adolescents from competitive sports-related SCD or ACA. One strategy may be to compare ECG findings between normal controls and patients with positive pathogenic variants without overt LVH using imaging techniques such as echocardiography.[30–32] A limitation of this strategy is the low penetrance of HCM during childhood.[31,32] Previous studies in children with positive mutations reported that 2 (17%) of 12 children (12±5 years old)[31] and 8 (7%) of 119 children (12±3 years old)[32] developed overt HCM during follow-up.

In the present study we used a unique strategy of retrospectively examining ECGs approximately 6 years before the actual HCM diagnosis to determine whether they fulfilled our voltage criteria. We used the 99.95th percentile (1:2,000) point as the voltage criterion for screening criteria, indicating that specificity was approximately 99.95% for all screening criteria. This strategy showed that 2 screening criteria (RI+SV3 and RV3+SV3) could predict a potential diagnosis of HCM in 5 of 9 patients (56% sensitivity) in the prediagnostic group. These patients did not fulfill the conventional criteria while in 1st grade, but showed a prominent LV wall thickness approximately 6 years later, suggesting that screening with voltage criteria is a useful strategy for the early screening of patients at risk of future marked LVH, although the efficacy was not optimal.

Both criteria included the SV3 (**Supplementary Table 2**). Of the 5 first graders in the post-diagnostic group who did not fulfill the conventional criteria, 3 fulfilled the voltage criteria that included SV3 or SV4 (**Supplementary Table 3**). In 7th and 10th graders in the post-diagnostic group, the highest sensitivity (44%) was found for RI+SV4, although nearly all patients met conventional criteria or had some abnormal findings. Our data suggest that the efficacy of the deep S wave in the mid-precordial leads shifts from V3 to V4 with age and/or with the development of HCM phenotypes. Our findings are consistent with reports that SD+SV4[13] or RI+SV4[14] were the most effective screening criteria for adult patients with LVH, both of which include SV4.

With regard to the effect of the R wave voltage, the voltage criterion of RV3+SV3 (effective for the prediagnostic group) showed a low sensitivity (20%) for patients who did not meet conventional criteria in 1st grade in the post-diagnostic group. Rather, the combined voltage criteria, including the R wave voltage in leads aVL or I, showed high sensitivity (**Table 4**). These findings are consistent with previous studies in adults showing the importance of the R wave in leads aVL[7] or I,[10,11,14] suggesting that the R wave vector progresses leftward and slightly upward of the frontal plane with age and/or phenotypic LVH progression.

The voltage criteria had a lower sensitivity for screening children and adolescents with HCM than the conventional criteria for the post-diagnostic groups. A potential reason for this is that the ECG may change with the development of the HCM phenotype. The QRS voltages of children and adolescents with HCM (**Supplementary Figure 2**), as well as those in the general population,[24] increase with age,

particularly in males. Nevertheless, only a small number of patients showed a constant increase in the QRS. Furthermore, many patients will develop HCM-related ECG abnormalities rather than an increase in QRS voltages after developing the HCM phenotype and pathological changes.

The present study showed that the voltage criterion of RV3+SV3 is effective in predicting a potential diagnosis of HCM in the 1st grade for the prediagnostic group. For the 1st grader's post-diagnostic group, 6 screening criteria, including RI+SV4, were candidates for screening 1st graders who did not meet conventional criteria. In the 7th and 10th grade screening programs, the conventional criteria may be sufficient, but the voltage criterion of RI+SV4 may be applicable in the 7th grade screening program because 14 of 32 (44%) patients in the 7th grade post-diagnostic group (**Figure 2**; **Table 4**) and 2 of 3 (67%) patients who did not fulfill the conventional criteria in the 7th grade post-diagnostic group fulfilled the criterion of RI+SV4. These data indicate that the voltage criteria of RV3+SV3 and RI+SV4 could be included in the 1st grade screening program and that the voltage criterion of RI+SV4 may be applicable to the 7th grade screening program.

This study has some limitations. First, the number of patients in the prediagnosis group was very small. Nevertheless, this is the first report examining the ECGs of patients 6 years before a diagnosis of HCM. Furthermore, our strategy was able to detect 5 of 9 patients (56%) with increased QRS voltages who did not meet conventional criteria. If we expand the number of patients using this strategy, the early diagnosis of HCM before the development of a phenotype may be possible. Second, we only presented tentative voltage criteria. QRS voltages have been reported to differ between races and/or studies.[19] Thus, future studies are required to develop the exact diagnostic voltage criteria for different races and/or ethnicities based on ECGs from their general populations. Third, the number of reference ECGs for the routine bandwidth was relatively small compared with that for the narrow bandwidth. This should be expanded in future studies. Finally, we did not discuss approaches to minimize the concerns of patients and families regarding the potential for developing HCM in the future. Further studies are required to confirm the sensitivity and specificity of our voltage criteria to provide sufficient information to minimize their concerns and develop requirements for follow-up.

In conclusion, early prediction of a potential diagnosis of HCM was possible using the voltage criterion of RV3+SV3 in >50% of patients in the 1st grade who were diagnosed in the 7th grade. This strategy may help prevent competitive activities-associated tragic accidents in these patients, although further prospective studies are required. For example, patients should be followed-up every few years, with the interval based on their ECG and echocardiography findings. Finally, the conventional criteria for HCM or abnormal findings can diagnose nearly all patients in the 7th and 10th grades.

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Disclosures

H. Tsutsui is a member of *Circulation Journal*'s Editorial Team. The remaining authors have no conflicts of interest to declare.

IRB Information

This study was approved by the Ethics Committee of the National Hospital Organization Kagoshima Medical Center (27-9 and 27-28).

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Supplementary Files

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COVID-19 with Rapid Progression to Hypoxemia Likely due to Imbalance between Ventilation and Blood Flow: A Case Report

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SAGE

Nobuyuki Koriyama, Akihiro Moriuchi, Kensaku Higashi, Tetsuro Kataoka, Takuro Arimizu, Go Takaguchi, Hideki Matsuoka and Maki Otsuka

National Hospital Organization Kagoshima Medical Center, Kagoshima, Japan.

ABSTRACT

BACKGROUND: In COVID-19 pneumonia, cases of severe hypoxemia in the early stage and cases of sudden deterioration in respiratory status due to silent hypoxia leading to death, have been reported.

CASE SUMMARY: A 70-year-old Japanese man with essential hypertension, dyslipidemia, chronic kidney disease and emphysema was hospitalized with the novel coronavirus disease. He had hypoxemia that was disproportionate to the severity of pneumonia indicated by computed tomography (CT), along with coagulation abnormalities. We speculated that there was a high possibility that he had developed ventilation and blood flow imbalance due to pulmonary intravascular coagulopathy (PIC) or hypoxic pulmonary vasoconstriction (HPV). In this case, early, short-term combination therapy with remdesivir, nafamostat mesylate and low-dose dexamethasone (Dex) was successful.

CONCLUSION: In COVID-19 patients with multiple comorbidities who have hypoxemia and coagulation abnormalities that are disproportionate to the severity of pneumonia on CT, it is important to commence antiviral and anticoagulant therapy as soon as possible, followed by use of a low dose of Dex.

KEYWORDS: COVID-19, hypoxic pulmonary vasoconstriction, pulmonary intravascular coagulopathy, remdesivir, nafamostat mesylate, dexamethasone

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CORRESPONDING AUTHOR: Maki Otsuka, Department of Hematology, National Hospital Organization Kagoshima Medical Center, 8-1 Shiroyama-cho, Kagoshima 892-0853, Japan. Email: otsuka.maki.we@mail.hosp.go.jp

Background

At the end of 2019, an outbreak of atypical pneumonia was reported in Wuhan City, Hubei Province, China. This pneumonia was shown to be caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and was named coronavirus disease 2019 (COVID-19). To date, the number of infected people globally is about 242 million, and the number of deaths is about 5 million. It is known that the disease is more likely to become severe in the elderly than in the young, and the mortality rate of people aged 80 years and over is extremely high, at 14.8 to 20.2%.[1,2] It has also been reported that there is a difference in mortality depending on the presence of underlying comorbidities, with reported mortality rates of 10.5% in patients with cardiovascular disease, 7.3% in diabetics, 6.3% in patients with chronic respiratory disease, and 6.0% in hypertensive patients.[3]

SARS-CoV-2 has a positive-sense, single-stranded RNA genome, and binds to angiotensin-converting enzyme 2 (ACE2) receptors present on the cell surface with a coronal spike protein on its surface envelope. By doing so, it invades the cell by endocytosis due to membrane fusion, leading to viral amplification.[4] ACE2 receptors are known to be widely expressed in nerve cells, olfactory nerve epithelium, the tongue, intestinal epithelial cells, vascular endothelial cells, etc, in addition to alveolar type II epithelial cells.[5,6] Therefore, SARS-CoV-2 causes not only severe pneumonia and fatal acute respiratory distress syndrome, but also multifaceted disorders in many cells, tissues, and organs.[7]

In COVID-19 pneumonia, cases of severe hypoxemia in the early stage[8] and cases of sudden deterioration in respiratory status due to silent hypoxia leading to death,[9] have been reported. It is speculated that major changes in one of the following factors: (1) thrombosis due to impaired blood coagulation, (2) disordered hypoxic pulmonary vasoconstriction (HPV),[10,11] and (3) imbalance between ventilation and blood flow in healthy lungs, or relatively small changes in these factors occurring at the same time[11] are responsible for the disease severity in such cases.

Here, we report a case of COVID-19 who showed progressive silent hypoxemia that was presumed to be due to an imbalance between ventilation and blood flow, but with only mild pneumonia visualized on computed tomography (CT), in whom early multidrug therapy was effective.

Case Report

The patient was a 70-year-old Japanese man (172.0 cm tall, weighing 68.0 kg, body mass index 23.0 kg/m^2) who had

Table 1. Laboratory findings on admission.

Peripheral blood	WBC	3270	/μL	
	NEUT (Neut)	5.94 (80.5)	×103/μL (%)	
	LYMPH (Lymph)	0.63 (8.5)	×103/μL (%)	[1.00 to 4.00 (18.0 to 50.0)]
	RBC	504	×104/μL	
	Hb	11.5	g/dL	[13.7 to 16.8]
	MCV	73.2	fL	[83.6 to 98.2]
	MCH	23	pg	[27.5 to 33.2]
	MCHC	31.4	g/dL	[31.7 to 35.3]
	HCT	36.9	%	[40.7 to 50.1]
	PLT	43.9	×104/μL	[15.8 to 34.8]
Coagulation	PT	90.4	%	
	PT-INR	1.05		
	APTT	29.5	sec	
	Fib	518	mg/dL	[200 to 400]
	FDP	5.26	μg/mL	[<5]
	D-D	1.68	μg/mL	[<1]
	AT-III	107.4	%	
Biochemistry	AST	14	U/L	
	ALT	8	U/L	
	LDH	202	U/L	
	ALP	248	U/L	
	γ-GTP	19	U/L	
	T. Bil	0.53	mg/dL	
	D. Bil	0.22	mg/dL	
	CK	59	U/L	
	TP	7.15	g/dL	
	Alb	4.16	g/dL	
	BUN	12.4	mg/dL	
	CRE	1.4	mg/dL	[0.65 to 1.07]
	eGFR	39.7	mL/min/1.73 m2	
	PPG	94	mg/dL	
	CRP	0.26	mg/dL	[0.00 to 0.14]
	Ferritin	7.37	ng/mL	[25.80 to 280.50]
	Presepsin	313	pg/mL	
	Fe	21	μg/dL	[40 to 188]
Urinalysis	Protein	(+)		
	Glucose	(-)		
	Occult blood	(-)		
Others	Influenza A Ag	(-)		
	Influenza B Ag	(-)		

The reference ranges of data showing abnormal values are shown in brackets. WBC, leukocytes; NEUT, neutrophils (absolute value); Neut, neutrophils (percentage); LYMPH, lymphocytes (absolute value); Lymph, lymphocytes (percentage); Mono, monocytes (percentage); Eosin, eosinophils (percentage); Baso, basophils (percentage); RBC, red blood cells; Hb, hemoglobin; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; HCT, hematocrit; PLT, platelets; PT, prothrombin time; PT-INR, prothrombin time-international normalized ratio; APTT, activated partial thromboplastin time; Fib, fibrinogen; FDP, fibrin/fibrinogen degradation products; D-D, D-dimer; AT-III, antithrombin III; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; γ-GTP, γ-glutamyltransferase; ChE, cholinesterase; T. Bil, total bilirubin; D. Bil, direct bilirubin; CK, creatine kinase; TP, total protein; Alb, albumin; Na, sodium; K, potassium; Cl, chloride; BUN, blood urea nitrogen; CRE, creatinine; UA, uric acid; eGFR, estimated glomerular filtration rate; PPG, postprandial blood glucose; CRP, C-reactive protein; Fe, iron; Ag, antigen.

smoked 20 cigarettes a day for 47 years until 5 years ago. He was under treatment and follow-up for essential hypertension, dyslipidemia and chronic kidney disease, and his blood pressure and lipid levels were well controlled with administration of 40 mg of olmesartan medoxomil (Olm) and 5 mg of atorvastatin calcium hydrate. His renal function was stable. The patient presented with nasal discharge, malaise and a mild cough, and tested positive for SARS-CoV-2 by the polymerase chain reaction (PCR) test three days after coming in extended contact with a colleague who was also diagnosed with SARS-CoV-2. Since he had many risk factors for disease aggravation, he was urgently admitted to our hospital (Day 1) the day after symptom onset and confirmation of the diagnosis.

At admission, his body temperature was 36.4 °C, blood pressure was 185/72 mm Hg, pulse was 86 beats/min, respiratory rate was 20 beats/min and peripheral oxygen saturation on pulse oximetry (SpO_2) was 97.0%. Laboratory findings at this time showed lymphocyte depletion and coagulation abnormalities [lymphocytes 8.5%, fibrinogen 518 mg/dL, fibrinogen degradation products 5.26 μg/mL and D-dimer (D-D) 1.68 μg/mL] (Table 1). In addition, iron deficiency anemia was observed (he was scheduled for close examination of the gastrointestinal tract after COVID-19 was cured), and hence, it was difficult to evaluate the clinical implication of the observed low ferritin level (Table 1). CT showed emphysematous changes in the lung field. Ground glass opacities with neither a crazy-paving pattern nor consolidation was found below the dorsal pleura of the upper right lobe, and the total CT score was 1/25 points (upper right lobe 1/5 points, middle lobe 0/5 points, lower right lobe 0/5 points, upper left lobe 0/5 points and lower left lobe 0/5 points), based on the scoring system described by Pan et al.[12] In addition, fibrosis, subpleural lines, the reversed "halo sign", pleural effusion and lymphadenopathy were not observed. It was considered to be a typical findings of early mild COVID-19 pneumonia (Figure 1a).

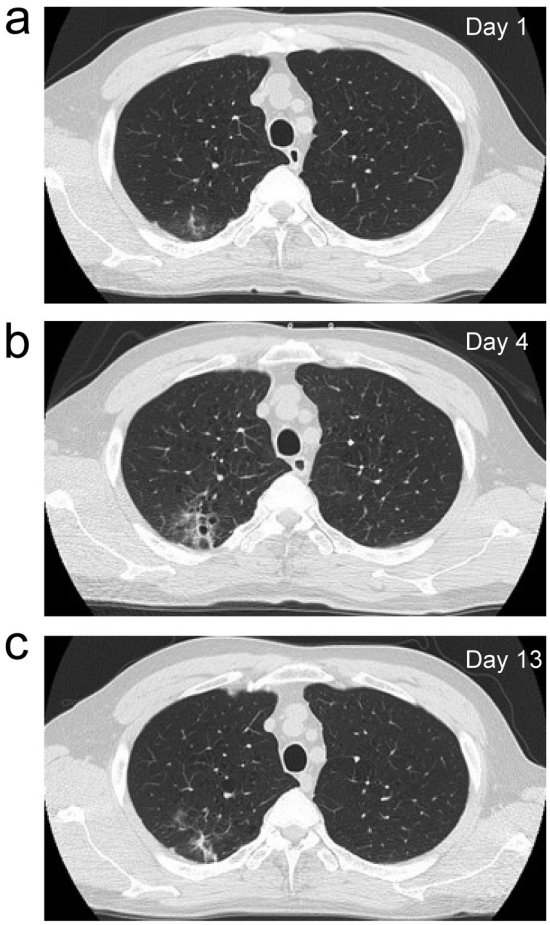

Figure 1. Chest computed tomography images. (a) Image taken on Day 1 showing emphysematous changes in the lung field and ground-glass opacities with unclear borders below the dorsal pleura of the upper right lobe (b) Image taken on Day 7 showing slight exacerbation of the ground-glass opacities. (c) Image taken on Day 13 showing improvement in the ground-glass opacities.

Although no decrease in SpO_2 was observed, administration of favipiravir (Fav) 3600 mg daily was started from the evening of the same day, due to the presence of mild pneumonia as seen on CT and the presence of multiple comorbidities. In addition, since SpO_2 decreased a little the following day, 1 L/min oxygen administration via a nasal cannula was also started. Weakness and a decreased level of consciousness (tendency to somnolence) appeared from the early morning of Day 2, but a neurologist ruled out stroke. Since somnolence and weakness were considered as side effects of Fav, the drug was discontinued on the evening of Day 2, and his symptoms improved by the morning of Day 3. Thereafter, since his temperature increased again, the frequency of administration of acetaminophen 500 mg was increased from 0 to 3 times a day. In addition, his CRP level increased and SpO_2 decreased, requiring an increase in oxygen flow rate from 1 to 3 L/min by nasal cannula. CT performed on Day 4 showed slight deterioration in the pneumonia. The total CT score was 2/25 points (ground-glass opacities only below the dorsal pleura of the upper right lobe) (Figure 1b). Therefore, 200 mg of remdesivir (Rem) was administered on Day 4, with 100 mg daily being administered from Day 5 until Day 10, for a total of seven days (Figure 2a). On Day 7, blood gas data under administration of 4 L/min oxygen by nasal cannula (Figure 2b) showed that the alveolar-arterial oxygen difference ($A\text{-}aDO_2$) had increased to 122.1 mm Hg (Table 2), indicating an imbalance between ventilation and blood flow. However, no pulmonary hypertension was observed on electrocardiogram or echocardiography. Furthermore, since a tendency of increasing D-D levels was also observed (Figure 2d), the combination of nafamostat mesylate (Naf) 100 mg daily by continuous intravenous infusion and dexamethasone (Dex) 6 mg daily was administered for four days from Day 7 (Figure 2a). The treatment was remarkably effective, resulting in fever reduction and a decrease in CRP and D-D levels (Figure 2a, c and d). On

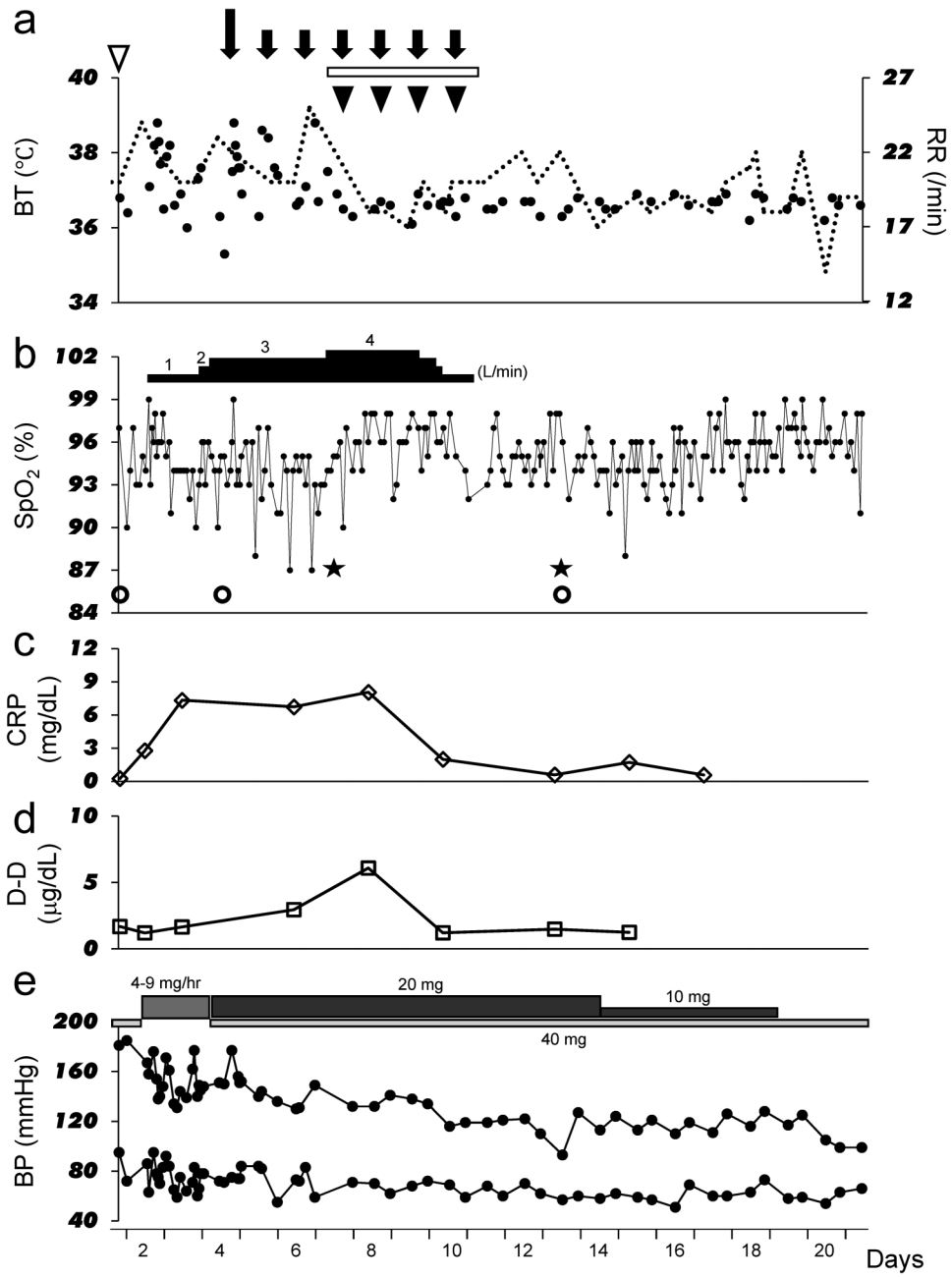

Figure 2. Clinical course of the patient. (a) The black dots indicate body temperature and dotted lines indicate respiratory rate. The white inverted triangle indicates 3600 mg favipiravir administration. The long downward-pointing black arrow indicates administration of 200 mg remdesivir, and the short downward-pointing black arrows indicate administration of 100 mg remdesivir. The horizontal white bars indicate continuous intravenous infusion of nafamostat mesylate 0.07 mg/kg/h. The black inverted triangles indicate administration of 6 mg dexamethasone. (b) Transition of SpO_2. The horizontal black bars indicate the flow rate of oxygen administered via a nasal cannula. The white circles indicate the day when CT was performed, and the black stars indicate the day when confirmatory blood gas analyses were performed. (c) Transition of C-reactive protein (CRP) levels. (d) Transition of D-dimer (D-D) levels. (e) Transition of systolic blood pressure at the top and diastolic blood pressure at the bottom part of the graph. The horizontal light-gray bar indicates administration of olmesartan, the moderately-dark gray bar indicates continuous intravenous infusion of pernidipine, and the dark gray bar indicates administration of nifedipine. BP, blood pressure; BT, body temperature; CRP, C-reactive protein; D-D, D-dimer; RR, respiratory rate; SpO_2, peripheral oxygen saturation on pulse oximetry.

Day 10, oxygen administration could be discontinued, and at the same time (Figure 2b), his blood pressure control improved (Figure 2e). By Day 13, A-aDO_2 had also significantly improved to 33.2 mm Hg without supplementary oxygen (Table 2), and CT showed a tendency for improvement in pneumonia. The total CT score at this time was still 2/25 points (ground-glass opacities only below the dorsal pleura of the upper right lobe) (Figure 1c).

For blood pressure control during the course of his hospitalization, continuous intravenous infusion of pernidipine

Table 2. Blood gas analysis.

	DAY 7	DAY 13		
O_2 NASAL (L/MIN)	4	0		
pH	7.398	7.462	μg/L	[7.36 to 7.44]
PCO2	33.1	32.4	mm Hg	[35 to 45]
PO2	96.2	76.4	mm Hg	[85 to 105]
HCO3-	20	22.6	mmol/L	[21 to 27]
BE	−4.1	−0.5	mmol/L	[−2.0 to 3.0]
A-aDO2	122.1	33.2	mm Hg	[<10]
Lac	2.2	1.7	mmol/L	[0.5 to 1.6]

The reference ranges of data are shown in brackets. pH, potential of hydrogen; PCO_2, partial pressure of carbon dioxide; PO_2, partial pressure of oxygen; HCO_3^-, actual bicarbonate; BE, actual base excess; A-aDO_2, alveolar-arterial oxygen difference; Lac, lactate. A-aDO_2 (Day 7) = [{ (760 − 47) × 0.21}-PCO_2/0.8] − PO_2
A-aDO_2 (Day 13) = [{ (760 − 47) × 0.364} − PCO2/0.8] − PO_2

(4-9 mg/h) was performed for two days when oral intake was difficult due to the decreased consciousness level, and from day 4, Olm 40 mg and nifedipine 20 mg were administered in combination. With the treatment of COVID-19, his blood pressure gradually stabilized, and the dose of nifedipine was reduced from Day 14 to 10 mg, and nifedipine was discontinued from Day 19 (Figure 2).

It took some more time for SpO_2 to stabilize, but it eventually improved and the patient was discharged on Day 21 (Figure 2).

Discussion

Cases of COVID-19 often develop ischemic stroke, ischemic heart disease and venous thromboembolism. Guan et al. reported that 46.4% of COVID-19 patients had elevated D-D levels.[13] It has been reported that elevated D-D is a predictor of COVID-19 mortality,[14,15] and that thrombi are frequently observed in pulmonary microarteries in autopsy cases.[16,17] Carsana et al. stated that the D-D value reached more than 10 times the upper limit of normal in all autopsy cases with COVID-19 for which D-D could be examined.[17] On the other hand, Asakura classified the type of disseminated intravascular coagulation (DIC) and reported "DIC with suppressed fibrinolysis" as a more serious condition. In their report, the increase in D-D remained relatively mild even in a serious case leading to death.[18] Furthermore, in an observational study of 183 COVID-19 patients in China, the mean D-D values in survivor and deceased groups were reportedly 0.61 μg/mL and 2.12 μg/mL, respectively.[19] In our case, the highest D-D level during his clinical course was 2.95 μg/mL, which was only a slight increase above the reference range. This suggests that in COVID-19 cases, the absolute value of D-D does not necessarily correlate with the severity of coagulation/fibrinolytic abnormalities, and hence, it is important to evaluate the pathological condition by confirming the transition of biochemical and fibrinolytic markers together.

McGonagle et al. distinguished macrothrombosis and widespread microthrombosis in the lung from DIC and called it pulmonary intravascular coagulopathy (PIC).[20] Causes of the blood coagulation disorders in COVID-19 include hyperformation of neutrophil extracellular traps due to inappropriate release of nuclear chromatin from activated neutrophils that migrated and accumulated at the infected site, and subsequent platelet aggregation by their supplementation/activation.[21,22] Furthermore, it is known that elevation of Von Willebrand factor (vWF), which is derived from macrophages and monospheres or is activated by inflammatory cytokines (Interleukin-6, Tumor necrosis factor-α, etc), coagulation-inducing factors such as factors VII and VIII, and plasminogen activator inhibitor-I, which suppresses urokinase-type or tissue plasminogen activator,[19,21] are involved in the pathogenesis. On the other hand, it has been reported that vWF and P-selectin are released into the blood due to activation and damage of vascular endothelial cells, or that the loss of thrombomodulin, which is the center of the fibrinolytic system, causes microvascular thrombosis.[23] Downregulation of ACE2 by SARS-CoV-2 binding inhibits the conversion of angiotensin II (AII) to angiotensin 1 to 7 (AT_{1-7}), resulting in an imbalance in the renin-angiotensin system. Reportedly, this results in further damage to vascular endothelial cells by AII, inflammation, promotion of oxidation, vasoconstriction, and coagulopathy mediated by an increase in plasminogen activator inhibitor-I.[24–26] In this case, the patient's blood pressure, which was largely stable at the time of admission, was subsequently elevated. It has been suggested that Olm increases ACE2 and AT_{1-7}, which binds to the Mas receptor to lower blood pressure and protect organs.[27] Due to the fact that blood pressure control was stabilized by the treatment of COVID-19 (Figure 2e), we speculated that the ACE2 consumption by SARS-CoV-2 might have made achievement of the antihypertensive effect of Olm via the Mas receptor difficult. On the other hand, the fact that blood pressure control was stabilized by the treatment of COVID-19 might suggest that direct vascular endothelial damage due to SARS-CoV-2 was progressing. In addition to the above-mentioned coagulopathy, the patient developed HPV disorder,[9,10] which, we speculated, together with emphysematous changes in the lungs, rapidly caused imbalance between ventilation and blood flow.

In this case, CT suggested pneumonia, which had multiple aggravating factors. Therefore, administration of Fav was started immediately after admission (Figure 2a). Fav selectively inhibits RNA-dependent RNA polymerase (RdRp) by its metabolism and conversion to the active form favipiravir-ribofuranosyl triphosphate by an intracellular enzyme, which is recognized as a substrate for RdRp by RNA viruses.[28] After the commencement of Fav treatment, the patient

exhibited weakness and decrease in consciousness (tendency to somnolence), which improved after discontinuation of Fav. Chen et al. reported that 4.31% of patients receiving Fav had a psychiatric reaction,[29] suggesting that these symptoms in our patient were likely to have been side effects of Fav. Subsequently, since fever persisted and the patient's SpO_2 progressively decreased (Figure 2b), Rem was started on Day 4 (Figure 2a). Reportedly, Rem is phosphorylated in cells to a nucleic acid analog (triphosphate type remdesivir), which, like Fav, binds to RdRp and selectively inhibits it, thereby suppressing the growth of RNA viruses.[28,30] Its effectiveness against SARS-CoV-2 by this mechanism has also been reported.[30–32] However, although CT suggested only slight exacerbation of pneumonia, our patient's fever persisted, SpO_2 decreased, and CRP and D-D levels tended to increase even after the start of Rem (Figure 2a to d). Therefore, Naf 100 mg and Dex 6 mg were also used from Day 8 (Figure 2a). Naf suppresses transmembrane protease serine 2 (TMPRSS2), an enzyme that cleaves and activates the spike protein, and blocks the invasion of SARS-CoV-2 into host cells.[28,33] It is used for the treatment of DIC and acute pancreatitis because it binds to the active center (serine) of enzymes such as thrombin, XIIa, Xa, VIIa, kallikrein, plasmin and trypsin, and suppresses the coagulation/fibrinolytic system. Doi et al. have reported the efficacy of Naf 0.2 mg/kg/h in combination with Fav for COVID-19 when administered as a continuous intravenous infusion for an average of 14 days,[34] but the optimal administration method has not yet been established. We were able to confirm a decrease in D-D levels after 4 days of administration of Naf with Rem at approximately the smallest dose (0.07 mg/kg/h) used in DIC (Figure 2d). Preliminary results from a large randomized controlled trial conducted in the United Kingdom showed that once-daily administration of 6 mg Dex for up to 10 days resulted in a 35% reduction in mortality in patients with COVID-19 receiving invasive mechanical ventilation.[35] On the other hand, the mortality rate in patients treated with Dex who received only oxygen support without invasive ventilatory management reduced by 20%.[35] Corticosteroids (CS) are known to bind to cytoplasmic CS receptors and translocate to the nucleus, reducing the activity of pro-inflammatory transcription factors, such as nuclear factor of κB and activator protein-1, and to regulate transcription of anti-inflammatory genes.[36] As a result, they reduce a number of inflammatory mediators involved in excessive cytokine responses (cytokine storms), although their effect on COVID-19 remains controversial.[37,38] Even in the large-scale randomized controlled trial mentioned above, no benefit of Dex administration to a group of patients with independent ventilation was recognized.[36] Since CS affects the function of many immune cells and suppresses both innate and acquired immunity, smaller doses and shorter treatment durations are recommended.[39] For this reason, we administered Dex 6 mg once daily for 4 days using a decrease in CRP as an indicator of response to therapy, which proved to be successful (Figure 2a). Asakura et al. have demonstrated the concept of antiviral, anticytokine and anticoagulant combination therapy according to the stage of COVID-19.[40] In our case, the combination therapy was extremely effective within a short period of time, confirming its importance in the treatment of COVID-19.

The limitations of our report are that we did not confirm the histopathology of the pulmonary pathology, and that since this was a case report, we cannot confirm that our therapy would be effective in all cases.

Conclusion

In COVID-19 patients with multiple comorbidities who have hypoxemia and coagulation abnormalities that are disproportionate to the severity of pneumonia on CT, there is a high possibility that ventilation and blood flow imbalance due to PIC or HPV disorder has occurred. We believe it is important to commence antiviral and anticoagulant therapy as soon as possible, followed by use of a low dose of Dex for a short period to control cytokine hyperreactivity.

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Author Contributions

N.K., AM, K.H., T.K., T.A., G.T., H.M., and M.O. attended to the patient; N.K. wrote the manuscript; M.O. supervised management of the case and contributed to writing and editing the manuscript. All authors have read and approved the final manuscript.

Informed Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

ORCID iD

Nobuyuki Koriyama https://orcid.org/0000-0002-4830-7154

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Original Article

An invaginated pancreaticogastrostomy following subtotal stomach-preserving pancreaticoduodenectomy: A prospective observational study

Teruo Komokata*, Kensuke Nuruki, Nobuhiro Tada, Ryo Imada, Bibek Aryal, Mamoru Kaieda, Soji Sane

Department of Surgery, National Hospital Organization Kagoshima Medical Center, Kagoshima, Japan

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ABSTRACT

Background/objective: Postoperative pancreatic fistula (POPF) leads to life-threatening complications after pancreaticoduodenectomy (PD). Pancreaticogastrostomy (PG) often adopted as a reconstruction technique after PD to prevent POPF. Delayed gastric emptying (DGE) following PD is the most common complication that compromises the quality of life. Subtotal stomach-preserving PD (SSPPD) preserves the pooling ability of the stomach and minimize the occurrence of DGE. This study aimed to describe our PG technique following SSPPD and evaluate the perioperative outcomes.

Methods: The study included patients who underwent PG following SSPPD from August 2013 to July 2020 at our institution. An invaginated PG was performed by one-layer eight interrupted sutures with a lost stent. Patients' demographics and perioperative outcomes were documented.

Results: This technique was applied in 72 patients with a median age of 75 years. The median operative time was 342 min. The clinically relevant POPF, DGE and post-pancreatectomy hemorrhage was 4 (5.6%), 5 (6.9%), and 10 (13.9%), respectively. Although the drain fluid amylase concentration on postoperative day 3 was significantly higher in clinically relevant POPF (CR-POPF) positive group (median, 2006 U/L vs. 74 U/L in CR-POPF negative group, $p = 0.002$), none of the risk factors including disease pathology, pancreatic duct diameter, texture of pancreas and excessive blood loss were significantly associated with CR-POPF. Other morbidity $\geq$ Clavien-Dindo classification II occurred in 29 patients (40.3%). The 90-days operative mortality was two (2.8%).

Conclusions: This novel method of one-layer invaginated PG following SSPPD is safe and dependable procedure with acceptable morbidity and mortality.

1. Introduction

Pancreaticoduodenectomy (PD) is the standard procedure of choice for pancreas head or periampullary tumors. Despite recent advances in surgical techniques and perioperative management, PD is still associated with substantial postoperative morbidity and mortality.[1,2]

Postoperative pancreatic fistula (POPF) remains a major concern that can lead to life-threatening complications such as post-pancreatectomy hemorrhage (PPH) and/or peritonitis[3,4]; therefore, it is crucial to use a surgical technique that reduces the risk of POPF. Recent randomized clinical trials and meta-analyses proposed that pancreaticogastrostomy (PG) substantially reduced the POPF rate compared to pancreaticojejunostomy (PJ).[5,6] However, in other prospective randomized trials, there was no statistical difference regarding POPF or overall complication rates between PG and PJ.[7,8] Although there is no clear consensus regarding the anastomotic technique, PG remains a preferred technique with some theoretical advantages over PJ among some surgeons.[9] Several PG techniques have been reported, including the one-layer invagination technique,[10] single purse-string suture duct to mucosa technique,[11] modified PG technique,[12] and binding invagination techniques with[13] and without[14] suturing the pancreas.

* Corresponding author. Department of Surgery, National Hospital Organization Kagoshima Medical Center, 8-1 Shiroyama-cho, Kagoshima City, 892-0853, Japan.
E-mail address: komokata.teruo.je@mail.hosp.go.jp (T. Komokata).

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However, no “gold standard” surgical technique has been established yet.

Subtotal stomach-preserving pancreaticoduodenectomy (SSPPD) was introduced during 1990's in Japan as an alternative to classic PD and pylorus-preserving PD (PPPD) to maintain the pooling ability of the stomach and reduce the incidence of delayed gastric emptying (DGE) by retaining most of the gastric body but resecting the pyloric complex.[15–19] While DGE is not a life-threatening complication of pancreatic surgery, it impairs quality of life, oral intake, increases hospital costs and delays the start of adjuvant chemotherapy, when required.

This study aimed to describe our PG technique following SSPPD and evaluate the perioperative outcomes.

2. Methods

This observational study was approved by the Institutional Review Board of National Hospital Organization Kagoshima Medical Center, Japan (approval number: #2020–13), and was registered in the clinical trials database UMIN-CTR (ID 000042500) on 19 November 2020. Written informed consent was obtained from all patients.

2.1. Study population and design

Between August 2013 and July 2020, a total of 86 patients received PD at our institution. After excluding patients receiving classic PD (n = 11) and laparoscopic SSPPD (n = 3), 72 (84%) consecutive patients who underwent PG following open SSPPD were included in this study. Background characteristics, surgical outcomes, and postoperative complications of the patients were retrospectively reviewed from the prospectively collected clinical database.

2.2. Surgical procedure

SSPPD was performed with a standard technique by dividing the stomach at 2 cm proximal to the pyloric ring and by transecting the pancreas at the level of portal vein with Thunderbeat® (Olympus Medical Systems Corp., Japan), and the specimen was assessed for pathology (Fig. 1a). A pancreatic tube (Sumitomo Bakelite Corp., Japan) 5–7.5 French in diameter was inserted into the main pancreatic duct of the remnant pancreas and fixed with an absorbable monofilament (4–0 PDS II®, Ethicon Inc., USA). Next, the posterior side of the pancreatic stump was mobilized for a distance of approximately 3 cm (Fig. 1b). A transverse full-thickness incision was made on the posterior wall of the stomach with a maximum length of equal to 3/4th the diameter of the pancreatic stump. Lesser and greater curvature side of the full-thickness layer of the stomach and the superior and inferior side of the full-thickness layer of the pancreas was sutured with a nonabsorbable monofilament (4–0 Prolene® SH, a curved 26 mm long needle, Ethicon Inc., USA), respectively. Additional three sutures of 4–0 Prolene® were placed from the posterior superior full-thickness layer of the stomach to the anterior parenchyma of the pancreas (Fig. 1c). The sutures on the pancreas were placed between 1 and 2 cm away from the cut edge. These sutures except for both edges were then ligated and the needle of the pancreatic tube was passed through the anterior wall of the stomach (Fig. 1d). Then, three sutures of 4–0 Prolene® were placed from the posterior inferior full-thickness layer of the stomach to the posterior parenchyma of the pancreas (Fig. 1e). Sutures on both edges were ligated while the pancreatic stump was invaginated into the gastric lumen by gently pulling the pancreatic tube and wrapping the posterior gastric wall around the pancreatic stump. After the remaining sutures were ligated, the pancreatic tube was cut and used as an internal stent (Fig. 1f). The entire procedure of this PG technique took around 10 min (data not shown) (Supplementary video 1-4). An end-to-side hepaticojejunostomy (HJ) and a stapled ante-colic side-to-side gastrojejunostomy (Powered ECHELON FLEX® gold cartridge 60 mm, Ethicon Inc., USA) with Braun anastomosis were performed to complete the reconstruction (Fig. 2). An enteral feeding tube was inserted at the distal side of the Braun anastomosis. An 8.0 mm Multi Channel® (Covidien Corp., Japan) drain was placed via the posterior side of the HJ into the superior side of the PG.

2.3. Postoperative management

All patients were managed with our standard algorithm for pancreatic resection. The nasogastric tube was removed principally on postoperative day (POD) 1 when the drainage amount was below 400 ml/day. Oral intake of liquid diet was encouraged on POD 3 to 5 and a solid diet was introduced over the following days. When oral intake was not feasible, enteral nutrition via a feeding tube was introduced. Amylase level was obtained from the drain on POD 1, 3, and 5. The abdominal drain was removed on POD 5 to 7, if there were no signs of pancreatic fistula or intra-abdominal collections. While proton pump inhibitor was routinely administered to reduce upper intraluminal PPH, octreotide was not given perioperatively.

2.4. Definitions

POPF was defined and graded according to the International Study Group of Postoperative Pancreatic Fistula (ISGPF),[20] as more than three times the serum concentration in drainage fluid on or after POD 3. The incidence of DGE was calculated according to the International Study Group of Pancreatic Surgery's (ISGPS) web-based calculator (http://pancreasclub.com/calculators/isgps-calculator/).[21] Since postoperative intra-abdominal complications such as POPF, anastomotic leakage, bleeding, ileus, fluid collection, or abscess formation are major causes of DGE, we defined DGE associated with those complications as secondary DGE, whereas DGE without any intra-abdominal complications was defined as primary DGE. PPH was defined and graded according to ISGPS.[22] Grades B and C POPF, DGE and PPH were defined as clinically relevant surgical complications. Postoperative complications apart from POPF, DGE and PPH were based on Clavien-Dindo classification (CDC).[23] CDC II or higher was considered significant. Operative mortality was defined as any death occurring within 90 days of surgery.

2.5. Statistical analyses

Statistical analysis was conducted with SPSS software (version 26; SPSS, Inc., Chicago, IL). Data were expressed as numbers with a percentage or median with range. The Kruskal–Wallis test was used to compare continuous variables and to interpret non-parametric variables. The Chi-square or Fisher's exact test was used to evaluate frequencies between categorical variables. A value of $p < 0.05$ was considered significant.

3. Results

3.1. Background characteristics and surgical outcomes

Background characteristics and surgical outcomes of the patients are listed in Table 1. There were 46 men and 26 women with a median age of 75 (range, 43–90) years. 30 (41.7%) patients received preoperative antithrombotic therapy with (n = 18) and without

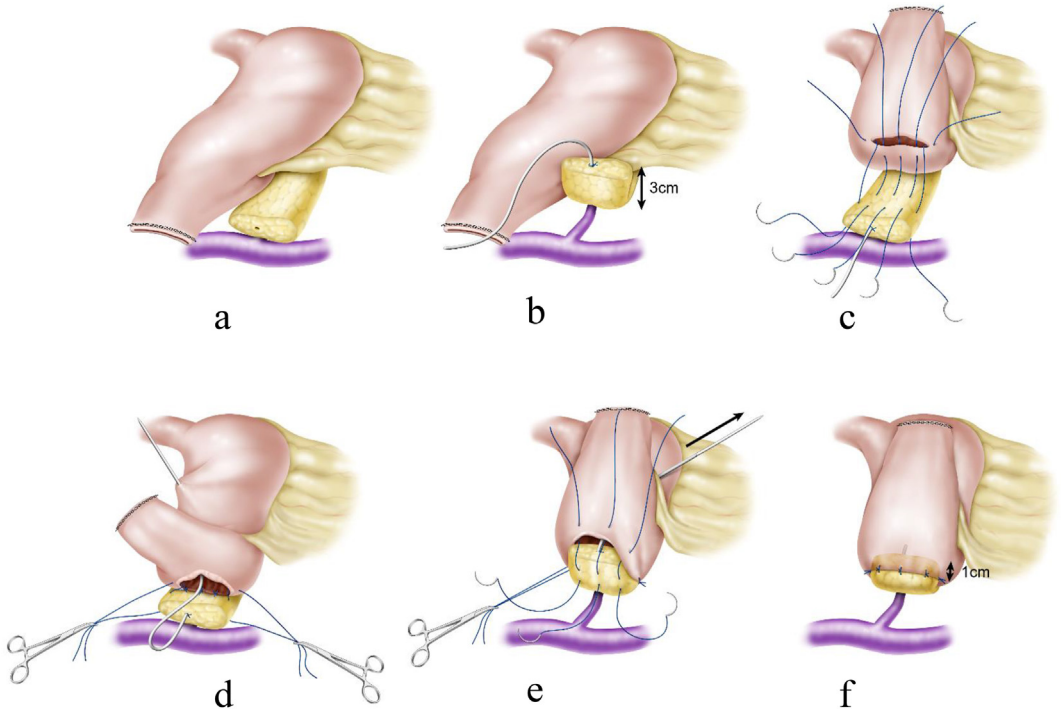

Fig. 1. Illustrations depicting the pancreaticogastrostomy technique. a: Completion of pancreatectomy. b: Insertion and fixation of the pancreatic tube and stump mobilization. c: One-layer interrupted sutures following transvers gastrectomy at the posterior wall of the stomach. d: The needle of the pancreatic tube was passed via the anterior wall of the stomach following ligation of three sutures except for both edges. e: After three additional sutures, the pancreatic stump was invaginated into the gastric lumen by gentle traction of the pancreatic tube and ligation of sutures on both edges. f: Completion of pancreaticogastrostomy.

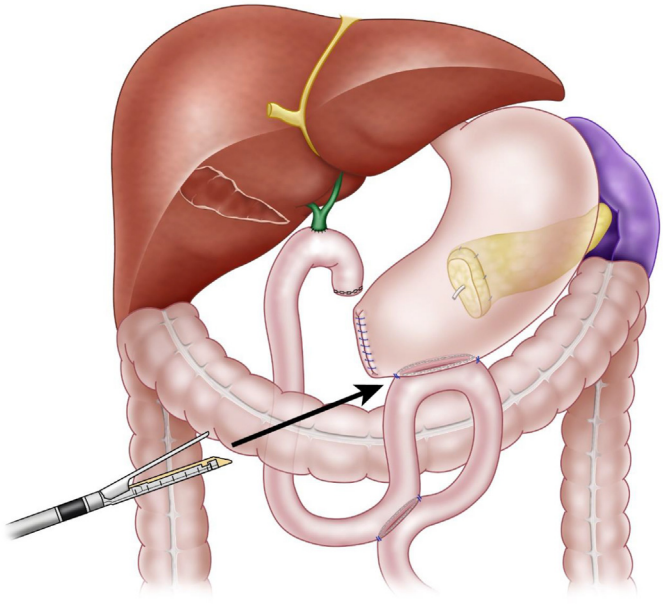

Fig. 2. Illustration depicting the completion of reconstruction following SSPPD.

Table 1
Background characteristics and surgical outcomes of the patients (n = 72).

Background characteristics	
Gender, male/female	46/26
Age (years), median (range)	75 (43–90)
BMI (kg/m^2), median (range)	22.0 (16.0–29.0)
ASA-PS score 1/2/3	4/49/20
Preoperative antithrombotic therapy, n (%)	30 (41.7)
Previous upper abdominal surgery, n (%)	15 (20.8)
Diseases, n (%)	
Pancreatic cancer	22 (30.6)
Bile duct cancer	19 (26.4)
Ampullary cancer	13 (18.1)
IPMN	10 (13.9)
Others	8 (11.1)
Surgical outcomes	72 (100)
Operation, n (%)	
Open SSPPD	
Additional visceral resection	12 (16.7)
PV reconstruction	8 (11.1)
Diameter of main pancreatic duct < 3 mm, n (%)	44 (61.1)
Texture of remnant pancreas, n (%)	
Soft	46 (63.9)
Firm	26 (36.1)
Operation time (min), median (range)	342 (213–550)
Blood loss (ml), median (range)	911 (270–3870)
Excessive blood loss (≥1000 ml), n (%)	29 (40.3)
Perioperative blood transfusion, n (%)	27 (37.5)

BMI: Body mass index; ASA-PS: American Society of Anesthesiologists Physical Status.
IPMN: Intraductal papillary mucinous neoplasm; SSPPD: Subtotal stomach.
-preserving pancreaticoduodenectomy; PV: Portal vein.

(n = 12) perioperative heparin bridging based on our hospital protocol.[24] The indication for surgery included pancreatic cancer in 22 (30.6%), bile duct cancer in 19 (26.4%), ampullary cancer in 13 (18.1%), intraductal papillary mucinous neoplasms in 10 (13.9%), and others in 8 (11.1%) patients. All patients underwent the open SSPPD and 12 (16.7%) patients underwent additional visceral resection including colectomy [n = 8, simultaneous colon cancer (n = 3), direct invasion into the colon or the vascular pedicle of the colon (n = 5)], splenectomy (n = 1, splenic artery aneurysm), and hepatectomy [n = 3, simultaneous gallbladder cancer (n = 2), intrahepatic cholangiocellular carcinoma (n = 1)]. 8 (11.1%) patients underwent portal vein resection and reconstruction. 61.1% of the

patients had a pancreatic duct diameter of less than 3 mm. The remnant pancreas was palpated by the surgeon to define the texture of the pancreas. 46 (63.9%) of them were soft and only 36.1% were firm consistency. The median operation time was 342 (range, 213–550) min. The median blood loss was 911 (range, 270–3870) ml and 27 (37.5%) patients required red blood cell transfusion until POD 1.94% of the patients were operated by a Board Certified Instructor in Japanese Society of Hepato-Biliary-Pancreatic Surgery.

3.2. Postoperative outcomes

Postoperative outcomes of the patients are listed in Table 2. POPF developed in 13 (18.1%) patients, with an incidence of clinically relevant POPF (CR-POPF) grade B (n = 4) or C (n = 0). The drain fluid amylase concentration [median (range)] on POD 3 in CR-POPF positive group was significantly higher: 2006 (609–10,526) compared to 74 (3–1163) U/L in CR-POPF negative group ($p = 0.002$). On the other hand, none of the risk factors including non-pancreatic cancer, diameter of main pancreatic duct <3 mm, soft texture of pancreas and excessive blood loss were significantly associated with CR-POPF. 5 (6.9%) patients developed grade B or C primary DGE. 10 (13.9%) patients had clinically relevant intraluminal (n = 8) or extraluminal (n = 2) PPH. Complications ≥ CDC II except for POPF, DGE and PPH occurred in 29 (40.3%) patients, including bile leakage (n = 5), surgical site infection (n = 5, superficial, n = 4, deep), cardio-cerebrovascular events (n = 5), pulmonary infection (n = 3) and others (n = 7). The 90-days operative mortality was 2 (2.8%); 1 patient (79 years old man) died of bile leakage and extraluminal grade C PPH on POD 22 and the other (83 years old man) died of non-occlusive mesenteric ischemia on POD 68.

4. Discussion

The present study demonstrated that a simple invaginated PG by one-layer eight interrupted sutures combined with SSPPD by side-to-side stapled ante-colic gastrojejunostomy and Braun anastomosis provided an acceptable incidence of CR-POPF (5.6%) and primary DGE (6.9%). These results suggest that this novel integrated technique is applicable not only in patients with high risks of CR-POPF including disease pathology, soft pancreas, small pancreatic duct and excessive blood loss during surgery but also in patients warranting shorter hospital stay and early initiation of adjuvant chemotherapy.

Table 2
Postoperative outcomes of the patients (n = 72).

POPF, n (%)	9 (12.5)
Grade A	4 (5.6)
Grade B	0 (0)
Grade C	5 (6.9)
Primary DGE (Grades B and C), n (%)	
PPH (Grades B and C), n (%)	8 (11.1)
Intraluminal	2 (2.8)
Extraluminal	
Postoperative complications (CDC ≥ II), n (%)	29 (40.3)
Bile leakage	5 (6.9)
Surgical site infection	5 (6.9)
Superficial	4 (5.6)
Deep	5 (6.9)
Cardio-cerebrovascular events	3 (4.2)
Pulmonary infection	7 (9.7)
Other complications	
ICU stay (days), median (range)	1 (1–18)
Length of hospital stay (days), median (range)	33 (19–344)
90 days-operative mortality, n (%)	2 (2.8)

POPF: Postoperative pancreatic fistula; DGE: Delayed gastric emptying.
PPH: Post-pancreatectomy hemorrhage; CDC: Clavien-Dindo classification.
ICU: Intensive care unit.

Although PJ is still a more commonly performed procedure in comparison to PG,[25] PG is being adopted by an increasing number of surgeons recently because of its several theoretical physiologic and technical advantages over PJ.[12,13] Pancreatic enzymes are inactivated by the acidic gastric fluid, and the deficiency of enterokinase in the stomach, which is necessitated for converting trypsinogen to trypsin and subsequent activation of other proteolytic enzymes, may prevent autodigestion of the pancreatic anastomosis. Besides, the alkaline pancreatic secretions may aid in preventing marginal ulceration. The anatomical proximity between the posterior gastric wall and the pancreatic remnant stump allows for potentially less tension on the anastomosis. Furthermore, excellent blood supply to the gastric wall enhances anastomotic healing, and the thickness of the gastric wall holds sutures well.

Several PG techniques have been described before.[11–14] However, those techniques involved binding invagination PG necessary for the distinct division of the anterior gastric wall that may lead to DGE and the duct-to-mucosa PG that may be often complicated and is a time-consuming procedure. In contrast, the present technique does not involve wide incision of the anterior gastric wall or stump of the remnant stomach and is notably simple and reproducible. The present PG technique is a modification of the technique described by Aranha[10] but with one-layer eight interrupted sutures between the full-thickness layer of the stomach and pancreatic parenchyma, which makes the anastomosis more robust. As the stomach has good distensibility with the excellent blood supply and the ligation knot always becomes the serosa or mucosa side of the stomach, invagination method by fixation with eight stitches following mobilization of the pancreatic stump and incision of the posterior gastric wall with a length of at most 3/4th the diameter of the pancreatic stump is appropriate even for soft and fragile pancreas.

One of the most common morbidities associated with pancreaticoduodenectomies is DGE, and SSPPD has been developed to prevent this troublesome complication.[15–19] Contrary to the expected outcome, in a recent meta-analysis, Hanna et al reported that DGE still occurs ranging from 5 to 59% following SSPPD.[26] We have identified three main reasons for the acceptable incidence of DGE (6.9%) in this present technique of PG in combination with SSPPD. First, the anterior wall of the stomach is not divided at all, evading restrains of the stomach peristalsis. In addition, this technique maintains a constant distance approximately 7–10 cm between PG and gastrojejunostomy, thus facilitating diet passage and preventing stricture formation of gastrojejunostomy. Second, side-to-side stapled gastrojejunostomy can hold the anastomotic lumen open uniformly, prevents anastomotic edema or stenosis efficiently, and avoids disturbance of the blood supply to the anastomotic site.[27,28] Third, ante-colic reconstruction with Braun jejunojejunostomy is thought to be an important procedure for reducing the risk of DGE.[29,30]

The present study possesses some limitations. First, it is a retrospective study conducted in a single institution. Second, clinically relevant PPH (13.9%) and the longer postoperative hospital stay (median, 33 days) appeared as a major concern. Clinically relevant PPH could be attributed to the patient population, especially thirty (41.7%) patients received preoperative antithrombotic therapy with and without perioperative heparin bridging. The longer postoperative hospital stay could have stemmed out of disparities in medical insurance system between Japan and the Western countries. Therefore, there are not a few patients performing it sequentially to rehabilitation.

5. Conclusion

This novel method of one-layer invaginated PG following SSPPD is safe and dependable procedure with acceptable morbidity and mortality. However, in order to elucidate the clinical benefits of this procedure, a well-designed comprehensive study would be desirable.

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Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.asjsur.2021.03.017.

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LETTER TO THE EDITOR

Anorectal function preserving surgery with endoscopic submucosal dissection in patients with perianal extramammary Paget's disease

Dear Editor,

Perianal extramammary Paget's disease (EMPD) is a rare malignancy that sometimes extends to the rectal mucosa and makes a complete histopathological resection challenging.[1] Among the therapeutic options for the management of perianal malignancy in the English literature, there is no evidence that an endoscopic submucosal dissection (ESD) is effective. Herein, we report two patients with perianal EMPD who were treated with ESD and underwent complete histopathological resection, leaving no anorectal dysfunction.

Case 1 was a 54-year-old woman with a perianal lesion extending to the dentate line (DL) who was diagnosed with EMPD (Figure 1a). We diagnosed primary EMPD based on immunohistochemistry results and colonoscopy that showed no evidence of colorectal cancer. The lesion, recognized as erythematous plaque, was excised with a 1-cm margin and the mucosal lesion was excised using the ESD technique above the muscle (Figure 1b). The defect was closed using a gluteal fold flap (GFF). No anal dysfunction persisted postoperatively. While histological examination revealed micro-invasive EMPD, no involvement of Paget's cells was seen at the surgical edge (Figure 1c–e).

Case 2 was a 62-year-old man diagnosed with recurrent perianal primary EMPD after a previous surgery who presented with a perianal lesion extending to the DL (Figure 1f). The lesion, recognized as erythematous plaque, was excised with a 1-cm margin, and the mucosal lesion was excised using the ESD technique above the muscle (Figure 1g). The defect was closed by rotating the previously used GFF on the first surgery. No anal dysfunction persisted postoperatively. Histopathological examination revealed no involvement of Paget's cells at the surgical edge.

Perianal malignancies, including EMPD, often extend to the rectal mucosa and make complete histopathological excision challenging. Although some patients undergo abdominal perineal resection as a surgical treatment for these malignancies,[2] this highly invasive surgery causes permanent anorectal dysfunction and could be an overtreatment for lesions without sphincter invasion.

Endoscopic submucosal dissection, a procedure for en bloc resection of gastrointestinal mucosal lesions, is a unique technique that enables resection of the mucosal lesion from an underlying muscle, which leaves the sphincter intact and preserves anal function.[3,4] ESD also makes it considerably easy to access the mucosal edge of the lesion. As lesions with submucosal invasion less than 1000 μm are suitable for ESD,[3] it is certainly convenient for mucosal resection of micro-invasive or intraepithelial EMPD. The most serious complications of this procedure are perforation and bleeding.[3] According to a report by Nakahara *et al*.,[5] an incisional distance within 2 cm from the dentate line to the oral side is recommended for a favorable postoperative anorectal function. Furthermore, en bloc resection allows accurate histological assessment which enables identification of the resection margins and reduces the risk of post-procedure recurrence.[3] The two patients presented in this report had pathologically negative margins with the application of ESD. Based on the histopathological negative margins and maintained anorectal function, we believe that ESD is the best modality to excise the extended mucosal lesion of EMPD without sphincter infiltration.

CONFLICT OF INTEREST

None declared.

Kentaro Yamamura[1]
Shigeto Matsushita[1]
Shunji Shimaoka[2]
Masaki Kitazono[3]
Takuro Maeda[4]
Kensuke Nuruki[5]
Shoichi Sakamoto[1]
Yoko Minokawa[1]
Megumi Aoki[1]

[1]*Department of Dermato-Oncology/Dermatology, National Hospital Organization Kagoshima Medical Center, Kagoshima, Japan*
[2]*Department of Gastroenterology, Nanpuh Hospital, Kagoshima, Japan*
[3]*Department of Surgery, Nanpuh Hospital, Kagoshima, Japan*
[4]*Department of Gastroenterology, National Hospital Organization Kagoshima Medical Center, Kagoshima, Japan*
[5]*Department of Surgery, National Hospital Organization Kagoshima Medical Center, Kagoshima, Japan*

Correspondence
Shigeto Matsushita, Department of Dermato-Oncology/Dermatology, National Hospital Organization Kagoshima

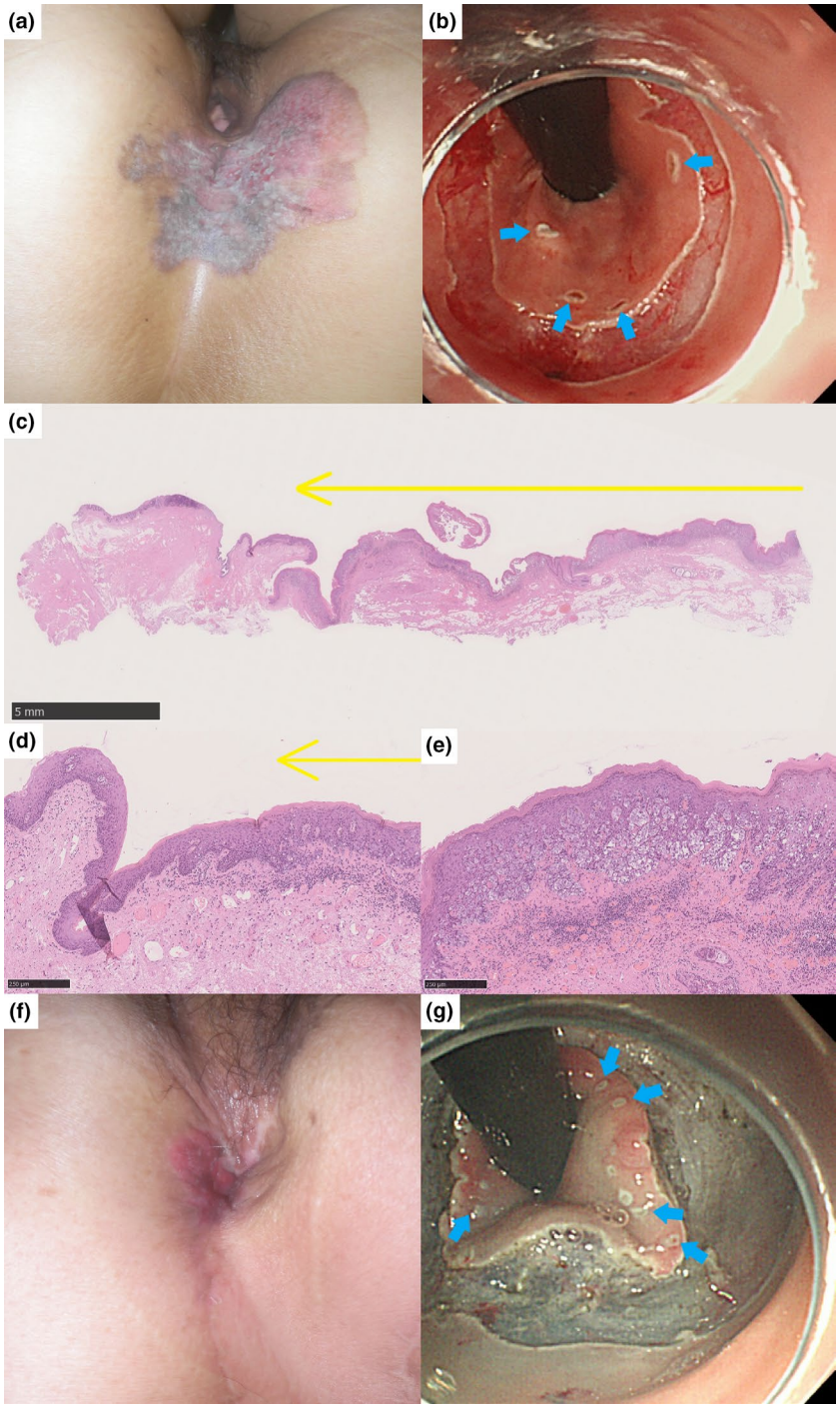

FIGURE 1 (a,f) Clinical findings of the two cases. An irregularly shaped plaque observed in the perianal region extending on the dentate line in each patient. (b,g) Intraoperative findings during the endoscopic submucosal dissection (views from the oral side of the rectus). The mucosal lesion, recognized as erythematous plaque extending from the anal canal, was dissected with a margin of 1 cm in the submucosal layer using a high-frequency knife in each patient. Clinically free margin of the lesion marked using hot forceps (showed in blue arrows). (c–e) Histopathological findings of the mucosal end in case 1. Nests of Paget's cells identified in the mucosa and superficial submucosa (area showed in a yellow arrow). No involvement of Paget's cells seen at the surgical edge

Medical Center, 8-1 Shiroyama-cho, Kagoshima 892-0853, Japan.
Email: shigeto0302@gmail.com

ORCID

Kentaro Yamamura https://orcid.org/0000-0003-1614-591X
Shigeto Matsushita https://orcid.org/0000-0003-2001-5341

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Research letter

Efficacy of S-1 plus docetaxel in the treatment of metastatic extramammary Paget's disease: a multicentre retrospective study

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Dear Editor, Metastatic extramammary Paget disease (EMPD) is an intractable condition refractory to conventional treatments; outcomes remain unsatisfactory.[1] Establishing an effective regimen with higher response rates and long-term efficacy is needed. Although our previous report described a patient with metastatic EMPD who responded to S-1 containing a 5-fluorouracil (5-FU) derivative plus docetaxel (DOC) combination chemotherapy (S-1/DOC),[2] little is known about the therapeutic efficacy of S-1/DOC in a large population. Therefore, in this multicentre retrospective study, we collected data from all patients (n = 12) with metastatic EMPD who received S-1 (80 mg m^{-2} daily for 14 consecutive days) and DOC (40 mg m^{-2} daily on day 1) at 2-week intervals at three institutes in Japan. The study was approved by the Institutional Review Boards and Human Research Ethics committees in each institution. Patient characteristics and best overall response are shown in Table 1. The most common metastatic sites were extraregional lymph nodes (seven patients). Ten patients (83.3%) received S-1/DOC as the first-line treatment, and two (16.7%) received the regimen as a second-line treatment after either combination of 5-FU, epirubicin, carboplatin, vincristine and mitomycin C (FECOM),[3] or DOC monotherapy with radiotherapy. The objective response rate (ORR) was 91·7% [complete response (CR) 16·7%; partial response (PR), 75·0%]. The median progression-free survival (PFS) and overall survival (OS) were 13·5 months [95% confidence interval (CI) 6·4–27.2] and 27·7 months (95% CI 13·0–39·3), respectively. The mean time to best ORR was 4·4 months (range 1–10). Nine patients (75%) experienced grade 3 and 4 adverse events (AEs), including leukopenia (n = 7), followed by neutropenia (n = 6), diarrhoea (n = 3), lymphopenia (n = 1) and grade 3 febrile neutropenia (n = 2). However, these events were manageable and no treatment-related deaths occurred. Owing to myelosuppression, dose reduction/interruption during consecutive administration of S-1 was necessary in seven patients (58.3%). However, these patients were able to continue treatment after modifications to the administration schedule. After discontinuation of S-1/DOC owing to disease progression, seven of 10 patients (70%) underwent postprogression therapy. In these patients, DOC monotherapy or gemcitabine was the most common treatment approach (two patients), followed by paclitaxel (PTX) monotherapy, PTX/trastuzumab or DOC/trastuzumab.

Several studies have reported FECOM, a combination of cisplatin and 5-FU (FP), and DOC monotherapy as key chemotherapeutic regimens,[3–6] with ORRs of 57%, 59% and 58%, median PFS rates of 6·5, 5·0 and 7·1 months, and median OS rates of 9·4, 12 and 16·6 months, respectively. S-1/DOC was superior to all other types of conventional chemotherapy reported previously. Regarding first-line treatment, DOC monotherapy is currently preferred based on its efficacy and tolerable adverse events. Although *Kato et al.* reported that the ORR after treatment with DOC was 50% in patients with inoperable lymph node metastases and 0% in those with visceral metastases,[6] in our study four patients had measurable visceral metastases alone and showed favourable responses, with an ORR of 75% (CR, n = 1; PR, n = 2; PD, n = 1). Four patients with extraregional lymph nodes metastases alone also showed favourable responses, with an ORR of 100% (CR, n = 1; PR, n = 3). As bone lesions were not

Table 1 Patient characteristics and best overall response

Characteristics	n = 12
Mean (range) age (years)	71·4 (54–91)
Male	7 (58.3)
Female	5 (41.7)
ECOG performance status	
0	11 (91.7)
1	1 (8.3)
≥ 2	0 (0)
Metastasis site	
Lymph node	7 (58.3)
Bone	4 (33.3)
Liver	3 (25)
Lung	2 (16.7)
Bladder	1 (8.3)
Line of treatment	
First	10 (83.3)
Second	2 (16.7)
Mean (range) duration of treatment (months)	13·9 (2·2–27·3)
Best overall response	
Complete response	2 (16.7)
Partial response	9 (75.0)
Stable disease	0 (0)
Progressive disease	1 (8.3)
Objective response	11 (91.7)

ECOG, Eastern Cooperative Oncology Group.

considered 'measurable' according to RECIST 1·1 and neither exacerbation nor new lesions were seen, the overall response in four patients with bone and extraregional lymph nodes or visceral metastases was assessed as a PR. Fukuda *et al.* reported a relatively good response to S-1/DOC as a salvage treatment in patients who failed to respond to another chemotherapy regimen.[7] However, a better response was seen in our study: 10 patients (83.3%) received S-1/DOC as the first-line treatment. Intriguingly, one patient with liver metastasis who was refractory to DOC monotherapy responded to S-1/DOC and achieved a CR. Wada *et al.* demonstrated that DOC showed synergistic antitumor and growth-inhibitory effects using S-1 by reducing 5-FU metabolites, thereby increasing 5-FU concentrations.[8] Hence, the patient who was refractory to DOC treatment responded favourably to S-1/DOC. Regarding toxicity, grade 3 and 4 AEs involving myelosuppression were seen in nine patients (75%), similar to DOC monotherapy.[5] Therefore, S-1/DOC may be beneficial as a first-line treatment, considering the balance between efficacy and toxicity. Our study had limitations related to the inherent issues of retrospective study designs and small sample sizes. Nevertheless, our study revealed that S-1/DOC may be more efficacious than conventional chemotherapy in patients with chemotherapy-naïve metastatic EMPD, with the potential to become a first-line treatment or key regimen in cases of DOC monotherapy failure. Future prospective studies with larger sample sizes are required to verify the chemotherapeutic efficacy of S-1/DOC and to establish a standard chemotherapeutic protocol for metastatic EMPD.

S. Matsushita,[1] K. Fujii,[2] I. Kajihara,[3] M. Aoki,[1] K. Yamamura,[1] K. Tada,[2] T. Kanekura,[2] J. Aoi[3] and S. Fukushima[3]

[1]*Department of Dermato-Oncology/Dermatology, National Hospital Organization Kagoshima Medical Center, Kagoshima, Japan;* [2]*Department of Dermatology, Field of Sensory Organology, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan; and* [3]*Department of Dermatology and Plastic Surgery, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan*

Email: shigeto0302@gmail.com

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