厚生労働科学研究費補助金
政策科学総合研究事業
（臨床研究等ICT基盤構築・人工知能実装研究事業）

安全な薬物治療をリアルタイムで支援する臨床決断支援システムの開発に関する研究

平成28年度～30年度　総合研究報告書

研究代表者　森　本　　剛

平成 31（2019）年　3 月

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（総合）研究報告書

安全な薬物治療をリアルタイムで支援する臨床決断支援システムの開発に関する研究

研究代表者　森本　剛　兵庫医科大学　医学部　教授

研究要旨

本研究は、電子カルテやオーダリングシステムから得られる患者の個別データのみならず、既に報告されている診療ガイドラインと患者背景や治療を組み合わせることで、個別の患者に最も適切な薬物治療をガイドする臨床決断支援システムを開発し、プロセスのみならず患者アウトカムを評価しようとするものである。

3年間の研究期間に薬物療法支援ガイドの開発及び診療プロセスガイドの作成を行い、これらのガイドを電子カルテ・オーダリングシステム上で利用するための臨床決断支援システムを開発した。本研究で開発された薬物療法支援ガイドは、腎機能に基づく薬剤投与量の推奨機能及び添付文書に基づく検査の推奨機能であり、作成された診療プロセスガイドは、多くの診療科が関わり、推奨が浸透しにくいと考えられるステロイド性骨粗鬆症のガイドラインに基づく薬物治療及び検査の推奨機能である。これらのガイドに基づいて臨床決断支援システムを開発し、島根県立中央病院の電子カルテ・オーダリングシステムに実装した。

臨床決断支援システムの有効性を評価するため、臨床決断支援システムの実装と同時に前向きコホート研究を開始し、当初の1年間は、臨床決断支援システムがバックグラウンドで稼働している状態（対照期間）における診療データの収集を行い、その後の1年間は臨床決断支援システムをバックグラウンドでの運用から実際に画面表示される運用に変更し、両期間において、臨床決断支援の機会及び内容、対象患者の背景や臨床検査値の変化、潜在的有害事象について分析した。バックグラウンド運用期間は1年間のデータが収集できたが、画面表示期間は画面表示開始から3ヶ月間のデータである（最終的には1年で完了予定）。解析対象となる外来受診患者総数は、バックグラウンド運用期間1年で37,093名（延べ受診回数209,522回）、画面表示期間3ヶ月で20,642名（延べ受診回数16,126回）であった。腎機能に基づく薬剤投与量の推奨機能による変更が8.8%、添付文書に基づく検査の実施率が0-67%、診療プロセスガイドによるビスホスホネート投与が7%、骨密度測定が12%認められ、これらの実施率は臨床決断支援システム導入前よりも改善していた。これらの結果より、臨床決断支援システムを導入することで、適切な診療を誘導できることが明らかとなった。今後、画面表示期間のフォローを通算1年まで実施し、解析を進めることで、プロセスのみならず、薬剤性有害事象などの患者アウトカムの改善を評価していく。

薬物療法支援ガイド及び診療プロセスガイドで構成された臨床決断支援システムを開発し、電子カルテ・オーダリングシステムに実装することで、診療プロセスや患者アウトカムを改善することができた。今回の研究を通じて、患者単位を対象とした安全なケアに人工知能が導入できる可能性が示唆された。今後、電子カルテ上の情報を適切に処理した上で人工知能を導入し、診療プロセス及び患者アウトカムを改善させる研究を継続したい。

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A. 研究目的

薬剤性有害事象は、医療行為による有害事象のうち最も頻度が高いことが報告されている（Leape LL. N Engl J Med 1991）。我々は薬剤性有害事象の多施設前向きコホート研究 Japan Adverse Drug Event Study（JADE Study）シリーズを実施し、例えば成人では、薬剤性有害事象は 100 入院患者あたり 29 件、1000 患者日あたり 17 件発生しており、多くの入院患者が何らかの薬剤性有害事象を経験していることを明らかにした（Morimoto T. J Gen Intern Med

2011)。更に、患者背景による薬剤性有害事象の発生頻度の予測（Sakuma M. Pharmacoepidemiol Drug Saf 2012）や薬剤性有害事象のハイリスク薬剤の同定（Sakuma M. J Patient Saf 2015）にも成功しており、これらの臨床疫学データを日常診療に活かす政策的臨床研究が喫緊の課題である。

本研究は、電子カルテやオーダリングシステムから得られる患者の個別データのみならず、既に報告されている診療ガイドラインと患者背景や治療を組み合わせることで、個別の患者に最も適切な薬物治療をガイドする臨床決断支援システムを開発し、これまでの研究と同様にプロセスのみならず患者アウトカムを評価しようとするものである。また、プロセスとしてのオーダーされた薬剤の種類や用量を評価するだけではなく、これまで研究代表者が実施してきた薬剤性有害事象研究の方法論に基づき、薬剤性有害事象や入院期間、死亡率などのアウトカムについても評価しようとする実証的な研究である。更に、臨床決断支援システムの導入前後のデータを用いて、臨床決断支援システムの費用効果性を評価することも目標とする。

B. 研究方法

3年間の研究期間に

1）薬物療法支援ガイドの開発
2）診療プロセスガイドの作成
3）臨床決断支援システムの開発
4）コホート研究での検証
5）システムの受け入れ度や費用効果性の分析

を行う。

1）薬物療法支援ガイドの開発

JADE Study及び島根県立中央病院の病院情報システムのデータを元に、薬剤使用パターンやハイリスクと考えられる薬剤の使用状況、リスクファクターなどの患者背景を抽出した。

加えて、添付文書の注意喚起については、全て遵守すべき内容ではあるものの、まずは薬剤の投与前、投与中に検査を要する注意喚起に注目した。添付文書上に投与前、投与中に検査に関する注意喚起について記載がある薬剤のうち、専門の診療科で通常実施しない検査項目は見落とす可能性があるのではないかという観点で対象薬剤を選択した。

2）診療プロセスガイドの作成

国内・海外における診療ガイドラインの分析や文献レビューを行い、オーダリングシステムに導入することで有効だと考えられる薬物治療について診療プロセスガイドを作成した。

3）臨床決断支援システムの開発

作成された薬物療法支援ガイド及び診療プロセスガイドを元に、島根県立中央病院の電子カルテ・オーダリングシステムに導入することで効果が期待される推奨機能やガイドを設計開発し、電子カルテ・オーダリングシステムに実装した。コホート研究を実施し、潜在的なガイド機会や対照となるデータを取得するため、1年間はバックグラウンドで稼働させ、実際の電子カルテ・オーダリングシステム画面にアラートは表示させない。

4）コホート研究での検証

臨床決断支援システム導入後より、全ての外来患者を対象に前向きコホート研究を開始した。研究期間は臨床決断支援システムが実装された後の24ヶ月であり、バックグラウンドで稼働される期間12ヶ月（バックグラウンド運用期間）と、実際に推奨画面が表示される期間12ヶ月(画面表示期間)に分かれる。

主要評価項目は、推奨医療（薬剤・検査）及び推奨診療ガイドラインの利用であり、副次評価項目は適正処方数、疑義照会件数、薬剤性有害事象の発生率、入院期間への影響、院内死亡率である。コホート研究として、対象患者の背景や臨床検査値などについても評価する。

5）システムの受け入れ度や費用効果性の分析

システムの受け入れ度を解析するための横断研究については、前向きコホート研究の途中で実施することによって、臨床医の行動に変化が生じ、前向きコホート研究データにバイアスが生じる可能性があるため、前向きコホート研究の終了後に全医師を対象とした横断研究を実施する。

方法は調査票を紙媒体で配布し、匿名回答とした上で、クロス集計を行う。主要アウトカムは臨床決断支援システムの使いやすさと受け入れ度とする。

費用効果分析については、薬剤性有害事象の減少効果を多変量モデルで算出し、診療報酬やその他の診療データを元に費用効果を分析する。

（倫理面への配慮）

前向きコホート研究は、通常の診療を行いながら、患者のデータを経時的に収集する観察研究であり、患者に対して直接的な介入は行わない。この研究を行うことで患者の診断や治療にマイナスの影響を及ぼすことは少なく、患者に健康上の不利益を与える可能性はない。逆に、本研究を実施することで患者の安全性がより高くなる可能性がある。

また、横断研究は匿名で実施し、さらに研究施設の管理者が情報に触れる可能性があることで、対象者の回答にバイアスがかからないようにするため、研究施設の担当者は調査票の配布は担当するが、回収には関与しない。

患者の診療データを扱うため、プライバシーの保護は厳重に行い、データの収集を行う施設（島根県立中央病院）とデータの解析を行う施設（兵庫医科大学）を分離し、データ収集施設から解析施設へのデータの送付時は、患者個人の同定及び連結が不可能な形で行われる。

本研究の実施については、兵庫医科大学及び島根県立中央病院における倫理審査委員会の承認を得た。また、本研究は「人を対象とする医学系研究に関する倫理指針」に厳正に則り施行する。島根県立中央病院においてはホームページ上に研究のお知らせを掲示し、オプトアウトをもって、研究参加への同意と見なす体制となっている。

C. 研究結果

1）薬物療法支援ガイドの開発

過去の「安全な薬物治療を促進する多職種間情報共有システムの開発に関する研究」で実施した入院患者における腎機能に基づく薬剤投与量の推奨の効果が明らかであったため、腎機能に基づく薬剤投与量の推奨を外来患者に拡大して実施することとした。

添付文書の注意喚起記載に基づいた薬物療法支援ガイドでは、投与前もしくは投与期間中に検査を行うことが推奨されている以下の 9 種類の医薬品についてについて臨床決断支援を行うこととした。

1. ビルダグリプチン：外来で過去 3 ヵ月間に、本薬剤の投与がない患者に本薬剤が処方された場合に、過去 3 ヵ月間の AST（GOT)、ALT（GPT)、γGTP、T-bil 検査の有無を検索し、1 項目でも検査がなければ検査実施を自動的に推奨する。また、その後の投与期間において、4 ヵ月を超えて同検査の実施がない場合においても、検査実施を自動的に推奨する。

＜根拠となった添付文書上の記載＞

（重要な基本的注意）

肝機能障害（肝炎を含む）があらわれることがあるので、本剤投与開始前、投与開始後１年間は少なくとも３ヵ月毎に、その後も定期的に肝機能検査を行うこと。（以下略）

2．パゾパニブ塩酸塩、レゴラフェニブ水和物、アキシチニブ、スニチニブリンゴ酸塩、ニボルマブ（遺伝子組換え）、ペムブロリズマブ（遺伝子組換え）、アテゾリズマブ（遺伝子組換え）：外来で本薬剤の投与を受けている患者について、過去3か月において、fT4、fT3、TSHのいずれの検査も実施されていない場合は、fT3、fT4及びTSHの検査実施を自動的に推奨する。

＜根拠となった添付文書上の記載＞

（重要な基本的注意：パゾパニブ塩酸塩）

甲状腺機能障害があらわれることがあるので、本剤の投与開始前及び投与期間中は定期的に甲状腺機能の検査を実施すること。本剤投与中に甲状腺機能障害が認められた場合は、適切な処置を行うこと。

（重要な基本的注意：レゴラフェニブ水和物）

甲状腺機能低下があらわれることがあるので、本剤投与中は定期的に甲状腺機能の検査を実施すること。甲状腺機能低下があらわれた場合には、適切な処置を行うこと。

（重要な基本的注意：アキシチニブ）

甲状腺機能障害（低下症又は亢進症）があらわれることがあるので、本剤の投与開始前及び投与期間中は定期的に甲状腺機能の検査を実施すること。本剤投与中に甲状腺機能低下症又は亢進症が認められた場合は、適切な処置を行うこと。

（重要な基本的注意：スニチニブリンゴ酸塩）

甲状腺機能障害（低下症又は亢進症）があらわれることがあるので、本剤の投与開始前に甲状腺機能の検査を行い、甲状腺機能障害を有する患者には投与開始前に適切な処置を行うこと。また、本剤投与中に甲状腺機能障害を示唆する症状が認められた場合は、甲状腺機能の検査を行うこと。なお、まれに甲状腺機能亢進に引き続き、甲状腺機能低下を認める症例が報告されているので、十分な観察を行い、適切な処置を行うこと。

（重要な基本的注意：ニボルマブ（遺伝子組換え））

甲状腺機能障害があらわれることがあるので、本剤の投与開始前及び投与期間中は定期的に甲状腺機能検査（TSH、遊離T3、遊離T4等の測定）を実施すること。本剤投与中に甲状腺機能障害が認められた場合は、適切な処置を行うこと。

（重要な基本的注意：ペムブロリズマブ（遺伝子組換え）

甲状腺機能障害、下垂体機能障害及び副腎機能障害があらわれることがあるので、定期的に甲状腺機能検査(TSH、遊離T3、遊離T4等の測定)を行い、患者の状態を十分に観察すること。また、必要に応じて血中コルチゾール、ACTH等の臨床検査、画像検査等の実施も考慮すること。

（重要な基本的注意：アテゾリズマブ（遺伝子組換え）

甲状腺機能障害、副腎機能障害及び下垂体機能障害が現れることがあるので、本剤の投与開始前及び投与期間中は定期的に甲状腺機能検査（ＴＳＨ、遊離Ｔ３、遊離Ｔ４等の測定）等を行い、患者の状態を十分に観察する（また、必要に応じて血中コルチゾール、ＡＣＴＨ等の臨床検査、画像検査等の実施も考慮する）。

3. アミオダロン塩酸塩：外来で本薬剤の投与を受けている患者について、過去 1 年間において眼科受診歴（細隙灯検査の実施）がない場合は、眼科受診を自動的に推奨する。

＜根拠となった添付文書上の記載＞

（重要な基本的注意）

本剤の投与に際しては、下記の重大な副作用及び発現頻度の高い副作用に十分留意し（副作用の項参照）、頻回に患者の状態を観察するとともに、脈拍、血圧、心電図検査、心エコー検査を定期的に実施すること。なお、諸検査は以下の表のとおり実施することが望ましい。

(4)眼

ほぼ全例で角膜色素沈着があらわれるが、通常は無症候性であり、細隙燈検査でのみ認められる。また、視覚暈輪、羞明、眼がかすむ等の視覚障害及び視神経炎があらわれることがある。

2）診療プロセスガイドの作成

本邦では高齢化に伴い骨粗鬆症患者が急増しているが、Common disease である同疾患の診療には専門医以外の多くの医師が携わっており、故に同疾患において適正医療が行われているかは不明である。また、長期ステロイド治療患者の 30～50%に骨折が起こるとの報告があり、ステロイド性骨粗鬆症は患者数が多く、また、小児から高齢者、閉経前女性や男性にも幅広く起き、それが社会生活へ影響する。また、原疾患の治療に携わる医師は骨粗鬆症の専門医ではない場合が多く、医師、患者ともにステロイド性骨粗鬆症に関する認識が高くないと考えられた。

そこで、原発性骨粗鬆症及びステロイド性骨粗鬆症の管理と治療のガイドラインを元に、電子カルテシステム上で推奨可能なアルゴリズムを作成し、それを診療プロセスガイドとして作成した。

骨粗鬆症ガイドライン（日本骨粗鬆症学会、2015）：図1、2に基づき、以下①②の推奨医療喚起を行う。

図1：原発性骨粗鬆症薬物療法開始基準（骨粗鬆症ガイドライン2015より）

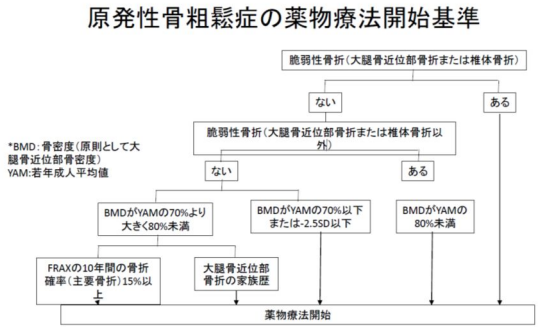
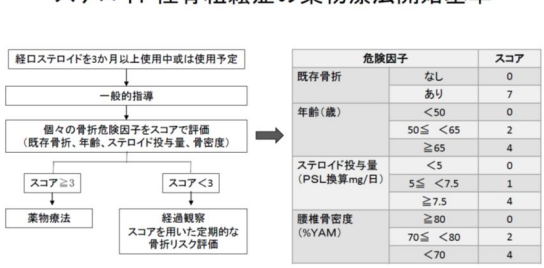


図2：ステロイド性骨粗鬆症の薬物療法開始基準（骨粗鬆症ガイドライン2015より）



① 対象：原発性骨粗鬆症又は骨粗鬆症の病名を有する患者

I. 過去１年以内に骨密度検査が無い場合

→骨密度検査を推奨

II. ビスホスホネート初回投与時*

→過去3か月以内に血清Ca，P，Mg，Cre，BUN及び骨密度検査が無い場合には同検査を推奨（*過去3か月に同処方の無い者）

② 対象：ステロイド性骨粗鬆症ハイリスク患者＝経口ステロイドを3か月以上使用中の外来患者

I． ステロイド性骨粗鬆症の薬物療法開始基準†に該当する場合
→ビスホスホネート処方を推奨
II．ステロイド性骨粗鬆症の薬物療法開始基準†に該当しない場合
→骨折歴確認を推奨
III.過去１年間に骨密度検査がない場合
→骨密度測定を推奨

†ステロイド性骨粗鬆症の薬物療法開始基準
1．ステロイド投与量（PSL換算）≧7.5mg/日
2．65歳以上
3．50歳以上＆ステロイド投与量（PSL換算）5mg/日以上
4．骨密度70%以下
5．骨密度70～80%＆ステロイド投与量5.0mg/日以上
6．骨密度70～80%＆50歳以上

3）臨床決断支援システムの開発

薬物療法支援ガイド及び診療プロセスガイドを元に、以下の臨床決断支援システムを島根県立中央病院の電子カルテシステムに実装し、バックグラウンドで稼働させた。

【腎機能に基づく薬剤投与量の推奨機能】

過去の「安全な薬物治療を促進する多職種間情報共有システムの開発に関する研究」で開発した、入院患者向けの腎機能に基づく薬剤投与量の推奨機能を踏襲した機能を開発し、外来患者においても腎機能に応じた推奨投与量が表示される（図 3）。推奨投与量が処方されない場合にはアラートが発動する。更に、処方から遡って過去 3 か月以内に腎機能評価や身長測定が無い場合にもアラートが発動する（図 4）。推奨投与量が表示される対象画面は外来処方指示、救命救急処方指示、外来処置（注射専用）指示、外来処置（注射専用）カレンダーである。

図3：推奨投与量のガイド

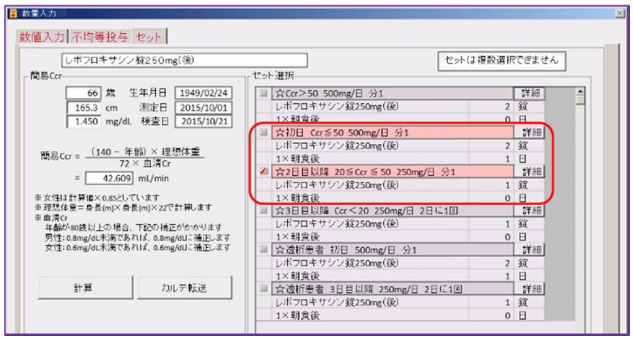
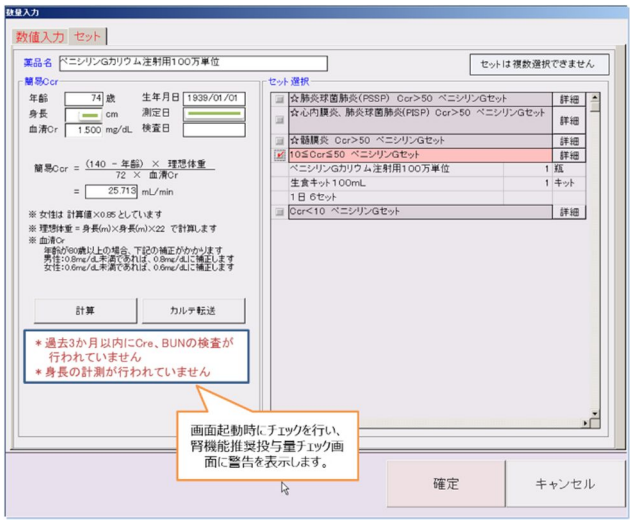


図4：腎機能評価及び身長測定のアラート



【添付文書に基づく検査の推奨機能】

添付文書の注意喚起記載に基づいた薬物療法支援ガイドでは、ビルダグリプチン、マルチキナーゼ阻害薬のパゾパニブ塩酸塩、レゴラフェニブ水和物、アキシチニブ、スニチニブリンゴ酸塩及び免疫チェックポイント阻害薬のニボルマブ、ペムブロリズマブ、そしてアミオダロン塩酸塩について臨床決断支援を行うこととした。

ビルダグリプチンは肝機能検査、マルチキナーゼ阻害薬及び免疫チェックポイント阻害薬は甲状腺機能検査、アミオダロンは眼科受診をしているかどう

かを判断し（図 5)、必要な検査を実施していない場合は、臨床決断支援システムから検査を連動してオーダーできるようにした（図 6)。

図5：対象薬剤投与時における検査のチェック画面

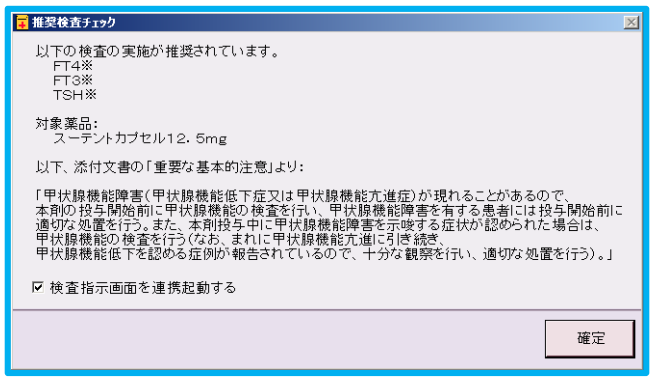


図6：チェック画面で、「検査指示画面を連動起動する」にチェックをした上で、確定を押すことで表示される検査オーダー画面

【原発性骨粗鬆症及びステロイド性骨粗鬆症のガイドラインに基づく薬物治療や検査の推奨機能】

ガイドラインに基づいて、以下の推奨機能を開発した。

原発性骨粗鬆症（図 7）

① 対象：原発性骨粗鬆症又は骨粗鬆症の病名を有する患者

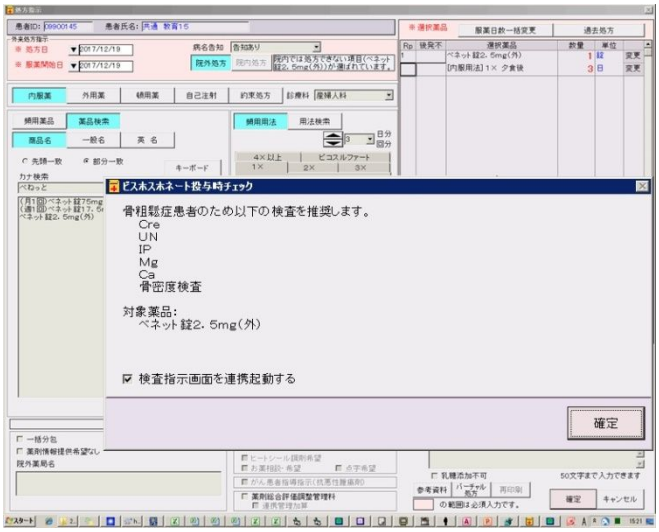
I． 過去１年以内に骨密度検査が無い場合

→骨密度検査を推奨

II．ビスホスホネート初回投与時*

→過去3か月以内に血清Ca，P，Mg，Cre，BUN及び骨密度検査が無い場合には同検査を推奨（*過去3か月に同処方の無い者）

図7：原発性骨粗鬆症に対する画面例



ステロイド性骨粗鬆症（図 8）

対象：ステロイド性骨粗鬆症ハイリスク患者＝経口ステロイドを3か月以上使用中の外来患者

I． ステロイド性骨粗鬆症の薬物療法開始基準†に該当する場合

→ビスホスホネート処方を推奨

II．ステロイド性骨粗鬆症の薬物療法開始基準に該当しない場合

→骨折歴確認を推奨

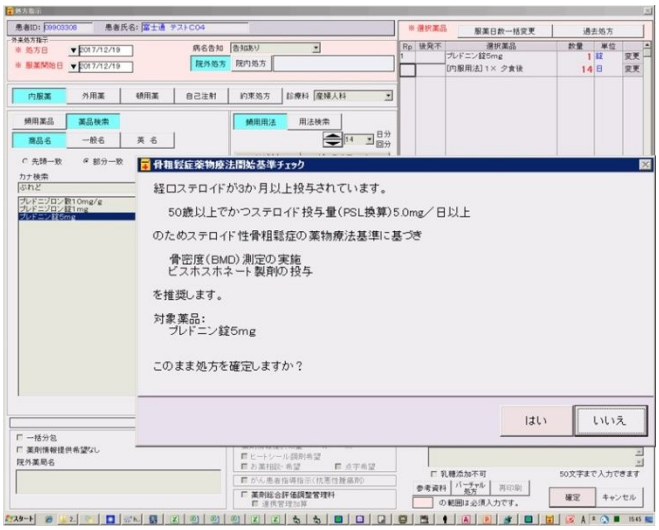
III．過去１年間に骨密度検査がない場合

→骨密度測定を推奨

†ステロイド性骨粗鬆症の薬物療法開始基準

1. ステロイド投与量（PSL換算）≧7.5mg/日
2. 65歳以上
3. 50歳以上＆ステロイド投与量（PSL換算）5mg/日以上
4. 骨密度70%以下
5. 骨密度70～80%＆ステロイド投与量5.0mg/日以上
6. 骨密度 70～80%&50 歳以上

図 8：ステロイド骨粗鬆症に対する画面例



4）コホート研究での検証

バックグラウンド運用期間の 1 年間(平成 29 年 10 月 1 日から平成 30 年 9 月 30 日まで）及び画面表示期間の 3 ヶ月間（平成 30 年 10 月 1 日から平成 30 年 12 月 31 日まで）において、対象となる外来受診患者総数はそれぞれ、37,093 名、20,642 名であった。また、延べ外来受診者回数は、バックグラウンド運用期間の 1 年間で 209,522 回、画面表示期間の 3 ヶ月間では、16,126 回であった。以下に患者背景の詳細を示す。

変数	バックグラウンド運用期間 (N=37,093)	画面表示期間 (N=20,642)
年齢（中央値、四分位）	57 (34，72)	60 (39，73)
65歳以上，n（%）	14,439 (39)	8,934 (43)
男性，n（%）	16,370 (44)	9,286 (45)
外来受診数（中央値、四分位）	4 (2，7)	2 (1，3)
入院歴，n（%）	7,827 (21)	2,222 (11)
喫煙歴，n（%）		
喫煙なし	17,485 (47)	10,037 (49)
過去喫煙	6,258 (17)	4,079 (20)
現喫煙	3,189 (9)	1,844 (9)
不明	10,161 (27)	4,682 (23)
既往歴，n（%）	15,265 (41)	9,911 (48)
家族歴，n（%）	1,411 (3.8)	917 (4.4)

稼働中の3つの臨床決断支援システムについて、バックグラウンド運用期間（1年間）と画面表示期間（画面表示開始後3か月間）における稼働状況を以下に示す。なお、バックグラウンド運用期間は、システムはバックグラウンドのみで稼働しており、潜在的な臨床決断支援の機会をモニタリングしている。実際の電子カルテ上には一切アラートが表示されないため、以後示すデータでは、バックグラウンド運用期間のデータについては、潜在的（支援開始後、臨床決断システムが顕在化して稼働する際に支援が表示される対象となる）事象のデータである。

【腎機能に基づく薬剤投与量の推奨機能】

腎機能に応じた推奨投与量をあらかじめ設定した、アラート対象処方を受けた患者数は、バックグラウンド運用期間は 6,331 人（17%)、画面表示期間は 3,595 人（17%)であった。そのうち、実際の処方

量が推奨投与量と異なるためにアラートが稼働した処方を、少なくとも 1 回は受けた患者は、バックグラウンド運用期間は 905 人（14%)、画面表示期間は 350 人（9%)であった。更に、アラート対象処方を受けた患者の、一人当たりの該当薬剤処方回数の中央値（最小値、最大値）は、バックグラウンド運用期間で 3 件（1，78)、画面表示期間は 2 件（1，24)であった。患者一人当たりが受けたアラート回数の中央値（最小値、最大値）は、それぞれ、0 件（0，22)、0 件（0，8)であった。

アラート対象処方の処方総数は、バックグラウンド運用期間は 34,074 件、画面表示期間は 8,440 回であった。このうち、アラートの稼働回数はバックグラウンド運用期間 2,552 件（7%)、画面表示期間は 511 件（6%)、推奨投与への変更を行った回数は、それぞれ 15 件（0.6%)、45 件（9%)であった。

外来通院中に一度でもアラート対象薬剤の投与を受けたことのある患者と、一度も投与のない患者、各群における、画面表示開始前後の腎機能のデータを以下に示す。

① BUN（mg/dl）値の推移

＊（ ）内は特記のない場合は中央値、四分位を示す

変数	バックグラウンド運用期間 (N=37,093)	画面表示期間 (N=20,642)
アラート対象薬剤を投与された患者数，n(%)	6,331 (17)	3,595 (17)
最大値	18.3 (14.3，23.9)	17.5 (14，22.6)
最小値	12.4 (9.6，15.7)	15.3 (11.9，19.1)
期間最初値	15.1 (12.1，19.2)	16.4 (13，20.7)
期間最終値	15.2 (12，19.5)	16.3 (13.1，21)
変化量（最大－最小）	5.3 (1.9，10)	0.7 (0，4.4)
変化量（最終－最初）	0 (-0.9，2.7)	0 (0，1)
アラート対象薬剤の投与がない患者数，n(%)	30,762 (83)	17,047 (83)
最大値	15.1 (11.8，19.4)	15.1 (12，19.3)
最小値	12.2 (9.2，15.5)	13.5 (10.5，17.2)
期間最初値	13.8 (10.8，17.5)	14.4 (11.4，18.4)
期間最終値	13.6 (10.6，17.3)	14.3 (11.3，18.1)
変化量（最大－最小）	1.3 (0，5.7)	0 (0，2.6)
変化量（最終－最初）	0 (0，0.6)	0 (0，0)

②Cr（mg/dl）値の推移

＊（ ）内は特記のない場合は中央値、四分位を示す

変数	バックグラウンド運用期間 (N=37,093)	画面表示期間 (N=20,642)
アラート対象薬剤を投与された患者数，n(%)	6,331 (17)	3,595 (17)
最大値	0.8 (0.7，1.1)	0.8 (0.7，1.1)
最小値	0.7 (0.6，0.9)	0.8 (0.6，1.0)
期間最初値	0.8 (0.6，0.9)	0.8 (0.7，1.0)
期間最終値	0.8 (0.6，0.9)	0.8 (0.7，1.0)
変化量（最大－最小）	0.1 (0.04，0.2)	0.02 (0，0.1)
変化量（最終－最初）	0 (-0.03，0.06)	0 (0，0.03)
アラート対象薬剤の投与がない患者数，n(%)	30,762 (83)	17,047 (83)
最大値	0.7 (0.6，0.9)	0.7 (0.6，0.9)
最小値	0.6 (0.5，0.8)	0.7 (0.5，0.8)
期間最初値	0.7 (0.5，0.8)	0.7 (0.6，0.9)
期間最終値	0.7 (0.5，0.8)	0.7 (0.6，0.9)
変化量（最大－最小）	0.03 (0，0.1)	0 (0，0.05)
変化量（最終－最初）	0 (0，0.02)	0 (0，0)

③EGFR（㎖/分/1.73㎡）値の推移

変数	バックグラウンド運用期間 (N=37,093)	画面表示期間 (N=20,642)
アラート対象薬剤を投与された患者数，n(%)	6,331 (17)	3,595 (17)
最大値	79.4 (63.2，96.7)	70.6 (55.6，86.7)
最小値	65.7 (49.8，81.2)	65.7 (50.7，80.6)
期間最初値	72.8 (56.8，88.7)	68.3 (53.5，83.8)
期間最終値	71.9 (56.2，87.8)	67.7 (52.8，83.2)
変化量（最大－最小）	10.9 (3.9，20.2)	1.4 (0，8.0)
変化量（最終－最初）	0 (-3.6，4.3)	0 (0，0)
アラート対象薬剤の投与がない患者数，n(%)	30,762 (83)	17,047 (83)
最大値	83 (66，103)	79 (62，97)
最小値	75 (58，93)	74 (58，92)
期間最初値	79 (62，98)	76 (60，94)
期間最終値	79 (62，97)	76 (60，94)
変化量（最大－最小）	2.3 (0，13.0)	0 (0，4.8)
変化量（最終－最初）	0 (0，1.0)	0 (0，0)

【添付文書に基づく検査の推奨機能】

対象薬剤と、推奨する定期検査を以下に示す。

注意喚起	薬剤名	対象検査項目
肝機能障害	エクア錠５０ｍｇ	AST、ALT，gGTP、T-Bilの全４項目
甲状腺機能障害	ヴォトリエント錠２００ｍｇ	TSH、fT3、fT4 のいずれか
	スチバーガ錠４０ｍｇ	
	インライタ錠１ｍｇ	
	インライタ錠５ｍｇ	
	スーテントカプセル１２．５ｍｇ	
眼障害	アミオダロン塩酸塩速崩錠１００ｍｇ	細隙灯検査
	アミオダロン塩酸塩速崩錠５０ｍｇ	

上記薬剤の処方を受けた患者数は、バックグラウンド運用期間は415人(1.1%)、画面表示期間は309人(1.5%)であった。そのうち、推奨検査が実施されていないために、検査推奨アラートを受けた患者数は、それぞれ、223人(54%)、149人(48%)であった。検査別では、眼検査推奨アラートを受けた患者数は、それぞれ、64人(29%)、45人(30%)、甲状腺機能検査推奨アラートを受けた患者数は、11人(4.9%)、2人(1.3%)、肝機能検査推奨アラートでは、155人(70%)、104人(70%)であった。以下に各薬剤別の処方数、アラート数、推奨検査実施数の詳細を示す。

①バックグラウンド運用期間

薬剤名	処方数 (n=2,266)	アラート数 (n=1,831)	検査数 (n=99)
エクア錠５０ｍｇ	1701	643 (38)	77 (12)
アミオダロン塩酸塩速崩錠 １００ｍｇ	311	271 (87)	7 (2.6)
アミオダロン塩酸塩速崩錠 ５０ｍｇ	140	118 (84)	3 (2.5)
スチバーガ錠４０ｍｇ	64	38 (59)	11 (29)
スーテントカプセル１２．５ｍｇ	39	6 (15)	0 (0)
ヴォトリエント錠２００ｍｇ	7	5 (71)	1 (20)
インライタ錠１ｍｇ	0	0 (0)	0 (0)
インライタ錠５ｍｇ	4	0 (0)	0 (0)

②画面表示期間

薬剤名	処方数 (n=590)	アラート数 (n=239)	検査数 (n=20)
エクア錠５０ｍｇ	452	149 (33)	15 (10)

アミオダロン塩酸塩速崩錠　１００mg	79	65（82）	2（3）
アミオダロン塩酸塩速崩錠　５０mg	32	22（69）	1（4.5）
スチバーガ錠４０mg	12	3（25）	2（67）
スーテントカプセル１２．５mg	12	0（0）	0（0）
ヴォトリエント錠２００mg	11	0（0）	0（0）
インライタ錠1mg	2	0（0）	0（0）
インライタ錠5mg	1	0（0）	0（0）

【原発性骨粗鬆症及びステロイド性骨粗鬆症のガイドラインに基づく薬物治療や検査の推奨機能】

① 原発性骨粗鬆症

研究期間に外来を受診した対象患者のうち、骨粗鬆症と診断されている患者は、バックグラウンド運用期間は411人(1.1%)、画面表示期間は325人(1.6%)であった。そのうち、過去１年以内に骨密度検査が実施されていないために、骨密度検査推奨アラートを受けた患者数は、それぞれ、313人(76%)、216人(66%)であった。

一方、対象患者のうち、ビスホスホネート初回投与（過去3ヶ月間に同処方がなされていない）が実施された患者は、バックグラウンド運用期間で131人(0.4%)、画面表示期間は59人(0.3%)であった。ビスホスホネート初回投与の時点で、過去3ヶ月以内に血清Ca，P，Mg，Cre，BUN及び骨密度検査が実施されていないために、同検査を推奨するアラートを受けた患者数はそれぞれ、127人(97%)、54人(92%)であった。

ビスホスホネート総処方数は、バックグラウンド運用期間は2,182件、画面表示期間は629件であった。このうち、初回投与にあたる処方件数は、それぞれ、136件(6%)、60件（10%)であり、これらの処方時に推奨検査が実施されていないために検査推奨アラートが稼働した回数は、バックグラウンド運用期間131件(96%)、画面表示期間は54件（90%)であり、アラート後に検査が実施された回数を確認すると、バックグラウンド運用期間は0件(0%)、画面表示期間は9件(17%)であった。

② ステロイド性骨粗鬆症

臨床決断支援の対象となる「3ヶ月以上にわたり使用されている経口ステロイド」に該当する処方を受けているステロイド使用患者（3か月以上）は、バックグラウンド運用期間では535人(1.4%)、画面表示期間は432人(2.1%)であった。骨粗鬆症診療ガイドライン2015に基づき開発された臨床決断支援システムにより、ビスホスホネート投与推奨アラートを受けた患者数は、上記対象患者のうち、それぞれ、306人(57%)、214人(50%)であった。更に、骨折歴確認推奨アラートは、画面表示開始前後で、それぞれ、139人(26%)、91人(21%)が対象となり、骨密度検査推奨アラートは、それぞれ、495人(93%)、374人(87%)が対象となった。

期間中のステロイド総処方数は、バックグラウンド運用期間は5,461件、画面表示期間は1,469件であり、そのうち、3ヶ月以上使用中のステロイド処方数は、それぞれ、3,752件(69%)、1,039件(71%)であった。これら、3ヶ月以上使用中のステロイド処方に対し表示されたビスホスホネート推奨投与アラート及び骨密度測定推奨アラートの詳細は以下である。

	バックグラウンド運用期間（N=37,093）		画面表示期間（N=20,642）	
	アラート数	処方数（検査）	アラート数	処方数（検査）
ビスホスホネート投与推奨	1,763	82（4.7）	478	33（7）
骨密度測定推奨	3,339	132（4.0）	766	91（12）

5）システムの受け入れ度や費用効果性の分析

システムの受け入れ度を解析するための横断研究ついては、前向きコホート研究の途中で実施することによって、臨床医の行動に変化が生じ、前向きコホート研究データにバイアスが生じる可能性があるため、前向きコホート研究の終了後に全医師を対象に実施する。

費用効果分析については、薬剤性有害事象の減少効果を多変量モデルで算出し、診療報酬やその他の診療データを元に費用効果を分析中である。前向きコホート研究の終了を待ち、モデルを用いた解析と並行して、本データを用いた解析も実施予定である。

D. 考察

本研究では、腎機能に応じた薬剤の推奨投与に関する支援、医薬品添付文書上の定期検査に関する支援、骨粗鬆症のガイドラインに基づく薬物治療や検査に関する支援で組み合わされた臨床決断支援システムを、電子カルテ・オーダリングシステムに導入することで、診療プロセスや患者アウトカムにどのような影響があるかについて評価した。

バックグラウンド運用期間及び画面表示期間のいずれの期間においても、外来患者背景に変化はなく、測定指標の変化は臨床決断支援システムの効果と判定してよいことが確認できた。

腎機能に応じた薬剤の推奨投与に関する支援では、アラート対象処方を受けた患者の割合は、画面表示開始前後ともに、全体の 17%と差はなく、アラート対象処方数におけるアラート稼働回数の割合も、画面表示開始前後でそれぞれ、7%、6%と差は認められなかった。アラートを受けた処方のうち、アラート後に推奨投与への変更を行った割合は、バックグラウンド運用期間は 0.6%、画面表示期間は 9%と、画面表示期間ではアラートの影響と考えられる推奨投与への変更が明らかに増加した。バックグラウンド運用期間では、システムはバックグラウンドの稼働のみで、実際にはアラートは表示されないため、バックグラウンド運用期間のデータに見られた、推奨投与への変更が行われた 0.6%は、アラートによらない、医師の自発的な処方変更であり、これがベースラインと考えられる。

更に、腎機能を示す検査値の推移については、画面表示期間のデータでは、変化量のばらつきが小さくなっているため、支援システムにより腎機能の悪化を防ぐことができていることが期待される。現時点では、画面表示期間のデータは画面表示開始後 3 ヶ月間のみの解析となっているが、今後、1 年間のデータがそろえば、腎機能保護におけるシステムの効果についても、明らかとなることが期待される。

医薬品添付文書上の定期検査に関する支援については、バックグラウンド運用期間の検査実施データが、医師の判断による自発的な検査実施のベースラインと考えられる。画面表示期間のデータは、3 ヶ月間のみであるが、バックグラウンド運用期間と比較して、検査頻度が上昇している傾向が認められ、対象薬品の薬剤性有害事象の予防及び早期発見、症状緩和への効果が期待される。

骨粗鬆症のガイドラインに基づく薬物治療や検査に関する支援については、今回のデータから、骨粗鬆症の病名が付いており、検査が必要であるにも関わらず、大半の患者が、推奨される検査を実施していないという現状が判明した。検査実施率については、その他の支援システムと同様、バックグラウンド運用期間の実施率4.3%が医師の自発的な検査実施率であり、ベースラインの検査頻度であると考えられる。画面表示期間は、3ヶ月間の時点で11%まで増加しているため、支援により検査実施率が向上していると考えられる。

骨粗鬆症患者へのビスホスホネート処方については、処方を受けている患者に関わらず、骨密度検査の実施割合はバックグラウンド運用期間でわずか3%、画面表示期間は8%程度という現状が判明し、治療中の骨粗鬆症患者においても、適切に骨密度検査が実施されていないことが懸念された。これについてのアラートの結果では、画面表示期間3ヶ月間のデータからも、アラート稼働回数の減少とアラートに対する検査実施の増加が認められ、臨床決断支援システムの効果が期待できる。

3ヶ月以上ステロイドを使用している患者では、ビスホスホネート処方が推奨されるものの、処方がされず、処方推奨アラートの対象となった患者の割合は、画面表示開始前後ともに40－50%と多く、また骨密度検査推奨アラートを受けた患者も、ともに90%前後と高い割合であった。画面表示期間については、アラートに応じた処方、検査実施の割合は増加しつつあり、1年後のデータ収集終了時の解析結果ではシステムの有効性が有意に示されることが期待できる。

厚生労働行政の観点においては、明確な指標が変化するなど、国民の目に見える形で医療の質が向上することが必要である。本研究によって、薬物療法支援ガイド、診療プロセスガイドを組み入れた臨床決断支援システムを電子カルテ・オーダリングシステムに導入し、日常診療で検証することができた。最終的な医師の受け入れ度やアウトカム評価は今後の解析が待たれるが、研究実施中における定性的な評価においては、医師の受け入れは順調であり、また、今回の分析データから、腎機能などの患者アウトカムも改善しており、臨床決断支援システムの有効性が期待される。

本研究で開発された臨床決断支援システムは、汎用性を高めるため及び論理式を確認するために明示的なガイドをマニュアルで作成し、導入した。このプロセスは人工知能を用いた診療支援のプロトタイプとなり、教師データとなる診療データの変数やターゲットとなるアウトカムを本研究の解析結果から見出すことで、人工知能を広く診療に展開することが可能である。

医療における人工知能の活用については、これまでは画像（CT 類、病理、皮膚、内視鏡）や診断（病名）が中心であり、教師データも比較的シンプルなものであった。今回の研究を通じて、患者単位を対象とした安全なケアに人工知能が導入できる可能性が明らかとなった。今後も研究を継続し、電子カルテ上の情報を適切に処理した上で人工知能を導入することで、診療プロセスを改善し、薬剤性有害事象の減少や、入院期間の短縮、院内死亡率の減少といった患者アウトカムの改善を目指したい。

E. 結論

薬物療法支援ガイド及び診療プロセスガイドで構成された臨床決断支援システムを開発し、電子カルテ・オーダリングシステムに実装することで、診療プロセスや患者アウトカムを改善することができた。今回の研究を通じて、患者単位を対象とした安全なケアに人工知能が導入できる可能性が示唆された。今後、電子カルテ上の情報を適切に処理した上で人工知能を導入し、診療プロセス及び患者アウトカムを改善させる研究を継続したい。

現在、国を挙げて、医療安全の推進及び医療における ICT の効果的な利用に取り組んでいるところであり、本研究を通じて、厚生労働省が進めている医療における ICT の有効活用のエビデンスを構築することができた。

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G. 知的財産権の出願・登録状況

1. 特許取得

該当なし

2. 実用新案登録

該当なし

3. その他

該当なし

平成30年度厚生労働科学研究費補助金
政策科学総合研究事業
（臨床研究等ICT基盤構築・人工知能実装研究事業）

安全な薬物治療をリアルタイムで支援する臨床決断支援システムの開発に関する研究

平成30年度第3回研究班会議

研究代表者

森本　剛

HYOGO COLLEGE OF MEDICINE

研究班構成・出席予定者

担当官庁

厚生労働省　大臣官房厚生科学課

藤巻　寿子　先生

江本　啓佑　先生

- 研究代表者
  - 森本　剛
- 分担研究者
  - 中村　嗣
  - 園山　智宏
  - 松本　知沙
  - 作間　未織
  - 太田　好紀
  - 武内　治郎
- 共同研究者
  - 綾仁　信貴
  - 村山　弘樹
  - 高橋　悠里
  - 岩崎　人士
  - 和田　隆平

HYOGO COLLEGE OF MEDICINE

議事

＜開会＞

ご挨拶・出席者紹介

【議題】

1.	研究の背景及び計画	森本
2.	導入された薬物療法支援ガイドー腎機能	太田
3.	導入された薬物療法ガイドー注意喚起対象薬剤	園山
4.	導入された診療プロセスガイド	中村
5.	導入前後のコホート研究データ	作間
6.	研究総括	森本
7.	総合討論	
8.	監督官庁からの総括コメント	

御礼

＜閉会＞

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平成30年度厚生労働科学研究費補助金
政策科学総合研究事業
（臨床研究等ICT基盤構築・人工知能実装研究事業）

安全な薬物治療をリアルタイムで支援する臨床決断支援システムの開発に関する研究

研究の背景及び計画

研究代表者

森本　剛

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第1回研究班会議議事録

【平成30年5月15日（火） 島根県立中央病院　会議室】

1. 中間データの確認及び修正
   - ✓ データ出力形式の確認
   - ✓ データ加工方式の確定
2. 臨床決断支援システムの表示スケジュール
   - ✓ 平成30年10月1日
   - ✓ 医療従事者向けの事前ガイダンス（9月）
3. 臨床決断支援システムの内容確認
   - ✓ 新規免疫チェックポイント阻害薬の追加
   - ✓ 甲状腺機能検査の項目追加（fT3）

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第2回研究班会議議事録

【平成30年11月13日（火） 熊本大学医学部　会議室】

1. 中間データの確認
   - ✓ 抽出データの確認
   - ✓ データ加工方式の修正
2. 臨床決断支援システムの開始後チェック
   - ✓ 平成30年10月1日開始より1ヶ月の経過
3. 論文化作業
   - ✓ 入院患者における多剤併用療法の影響

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平成30年度の研究結果

- 臨床決断支援システムの導入
  - 外来患者対象
  - 薬物療法支援ガイド
    - 腎機能別推奨投与量
    - 注意喚起対象薬剤
  - 診療プロセスガイド
    - 骨粗鬆症ガイドライン
- 前向きコホート研究
  - アウトカム
    - プロセス
    - 患者アウトカム

HYOGO COLLEGE OF MEDICINE

Taipei Municipal Wanfang Hospital Meeting
March 5–6, 2019

Effectiveness of clinical decision support system

Takeshi Morimoto, MD, PhD, MPH

Professor of Medicine, Department of Clinical Epidemiology

Vice-Director, Center for Clinical Research and Education

Staff Physician, Division of General Internal Medicine

Hyogo College of Medicine and Hospital

Research Lead, Research Group on Deployment

of ICT/AI in Clinical Practice, Ministry of Health, Japan

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臺北市立萬芳醫院 - 委託財團法人臺北醫學大學辦理
Taipei Municipal Wanfang Hospital (Managed by Taipei Medical University)

Welcome Schedule

Date：2019 /03 / 05　Tuesday
Time：09:00 – 09:30
Place：Meeting Room 3th

Guests：

1. Takeshi Morimoto, Professor of Medicine, Hyogo College of Medicine
2. Mio Sakuma, Senior Assistant Professor of Medicine, Hyogo College of Medicine
3. Tsukasa Nakamura, Director, Shimane Prefectural Central Hospital
4. Nobutaka Ayani, Senior Assistant Professor of Medicine, Kyoto Prefectural University of Medicine

Attendees：

1. Ta-Liang Chen, M.D., Superintendent
2. Yu-Ting Tai, M.D., Director of Medical Quality Department
3. Laura Cheng, Manager of Education and Research, Department of Pharmacy
4. Roger Wu, Manager of International Medical Center

Program：　※Language：English

Time	Schedule	Place
09：00-09：05	Welcome Note	3th Meeting Room
09：05-09：15	Introduction of Wanfang Hospital	
09：15-09：25	Medication Safety System in Wanfang Hospital (Department of Pharmacy)	
09：25-09：30	Discussions and Group Photo	

OF MEDICINE

臺北市立萬芳醫院 - 委託財團法人臺北醫學大學辦理
Taipei Municipal Wanfang Hospital (Managed by Taipei Medical University)

Welcome Schedule

Date：　2019 /03 / 06　Wednesday
Time：　14:00 – 16:30
Place：　Meeting Room 7
Guests：

1. Takeshi Morimoto, Professor of Medicine, Hyogo College of Medicine
2. Mio Sakuma, Senior Assistant Professor of Medicine, Hyogo College of Medicine
3. Tsukasa Nakamura, Director, Shimane Prefectural Central Hospital
4. Nobutaka Ayani, Senior Assistant Professor of Medicine, Kyoto Prefectural University of Medicine

Attendees：

1. Ming-Chih Yu, M.D., Deputy Superintendent
2. Tso-Hsiao Chen, M.D., Deputy Superintendent
3. Yu-Ting Tai, M.D., Director of Medical Quality Department
4. Mei-Fang Chen, Manager of Patient Safety Section
5. Roger Wu, Manager of International Medical Center

Program：　※Language：English

Time	Schedule	Departments	Place
14：00-14：05	Welcome note	WanFang Hospital	7th Meeting Room
14：05-14：45	AERS system in Wanfang Hospital	Medical Quality Department	
14：45-15：25	CDSs(Clinical decision support system) effectiveness in hospital inpatients	Hyogo College of Medicine	
15：25-16：20	Cooperation Discussions	WanFang Hospital	
16：20-16：30	Group Photo	WanFang Hospital	

E OF MEDICINE

Members of Research Group

- Research Lead
  - **Takeshi Morimoto** (Hyogo College of Medicine)
- Members
  - **Tsukasa Nakamura**, Tomohiro Sonoyama, Shinji Kosaka (Shimane Prefectural General Hospital)
  - **Mio Sakuma**, Yoshinori Ohta, Jiro Takeuchi, *Graduate Students* (Hyogo College of Medicine)
  - Chisa Matsumoto (Tokyo Medical University)
  - **Nobutaka Ayani** (Kyoto Prefectural University of Medicine)
  - Techno Project Japan Co.
  - Nexis Co., Ltd.

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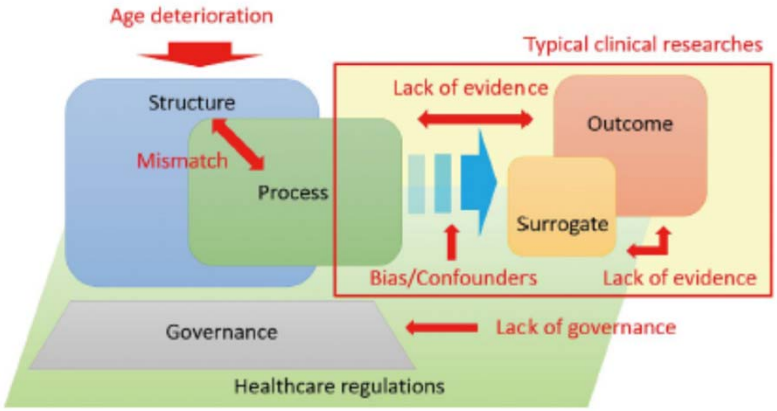
Both Process and Outcomes



（Morimoto T. ***Circ J*** 2015）

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Our Journey on Quality of Care

2002 2004 2006 2011 2012 2014 2016 2019

Return from Harvard

Start Japan Adverse Drug Event (JADE) study

Publish Prototype of Decision Support

Publish JADE-Adult

Publish JADE-ICU

Publish JADE-Pediatrics

Publish JADE-Psychiatric

Start Japan adverse EvenT (JET) study

Start Decision Support study for inpatients

Start Decision Support study for outpatients

HYOGO COLLEGE OF MEDICINE

Leading Center in Japan

- **Nakamura T**, Takahashi O, Matsui K, Shimizu S, Setoyama M, Nakagawa M, Fukui T, ***Morimoto T**. Clinical prediction rules for **bacteremia and in-hospital death based on clinical data** at the time of blood withdrawal for culture: an evaluation of their development and use. ***J Eval Clin Pract*** 2006;12:692-703.
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Leading Center in Japan

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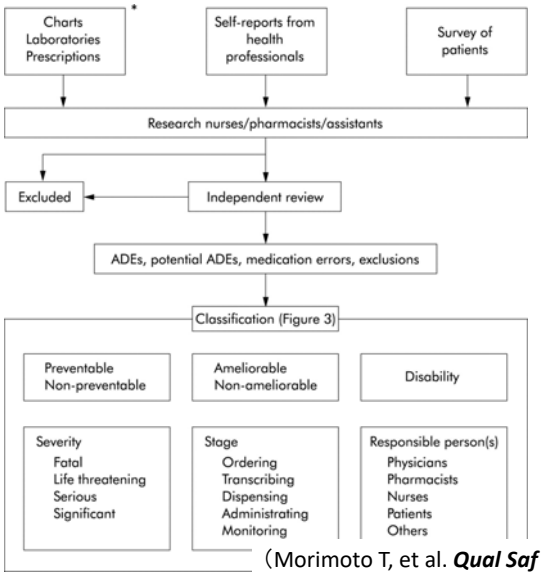
JADE Study & JET Study



BMJ Quality & Safety

(Morimoto T, et al. ***Qual Saf Health Care*** 2004)

Our Directions

No Computerized Support
All Potential ADEs Scrutinized
Comprehensive Collection
Manually Reviewed

Decision Support
Prespecified ADEs
Laboratory and Process
Automated Collection

Illustration by Chris Gash

HYOGO COLLEGE OF MEDICINE

In Addition To

- Electronic Health Records
  - Electronic Incident Reporting
- Computerized Physician Ordering Entry
  - Electronic Drug Formula References
  - Drug-Drug Interaction/Drug Allergy Alert
  - Electronic Clinical Pathways
- Bar-coding
  - Patient / Medication

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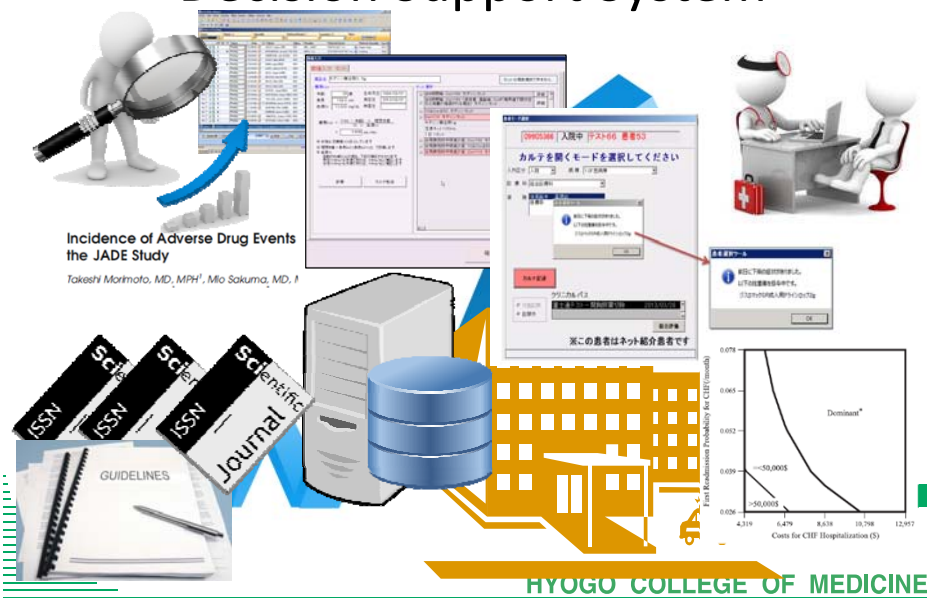
Decision Support System



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JADE Study

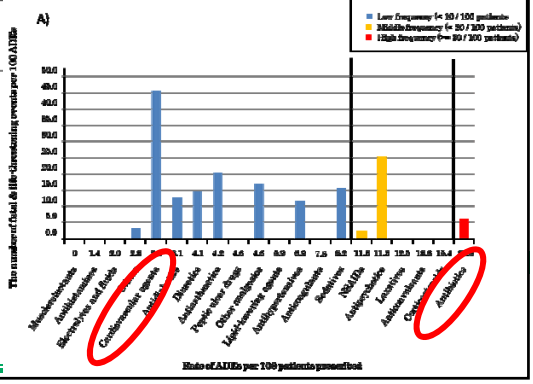
Table 1. Incidence of Adverse Drug Events

Ward	n	Patient-days	ADEs	Incidence*	95% CI	Crude rate†	95% CI	Annual ADEs‡
Medicine	1,531	25,734	504	19.6	17.9-21.3	32.9	30.6-35.3	4,148
Surgery	1,469	30,419	407	13.4	12.1-14.7	27.7	25.4-30.0	3,218
ICU	459	3,230	99	30.7	24.6-36.7	21.6	17.8-25.3	634

*ADE, adverse drug event; ICU, intensive care unit; CI, confidence interval; *per 1,000 patient-days; †per 100 admissions; ‡Extrapolated from number of ADEs and information from three hospitals*

Table 5. Stages of Primary Errors Associated with Preventable and Potential Adverse Drug Events

Event	Ordering n (%)	Transcription n (%)	Dispensing n (%)	Administration n (%)	Monitoring n (%)
Preventable ADEs	49 (35)	0 (0)			
Intercepted potential ADEs	88 (90)	0 (0)			
Nonintercepted potential ADEs	182 (76)	2 (0.8)			
All above events	319 (66)	2 (0.4)			



- ✓ Frequent Adverse Drug Events
- ✓ Most Error Occurred at Ordering Stage by Physicians
- ✓ Risk for Severity Varies between Medication

（Morimoto T. ***J Gen Intern Med*** 2011; Sakuma M. ***J Patient Saf*** 2015）

Decision Support System for Inpatients

（Funded by Government 2014-2015）

Guided Medication

Doses based on

Recent Renal Fx

Deploy

−3M → Time 0 → +3M

Before	After
3,203 Patients	3,237 Patients
46,369 Patient-days	46,536 Patient-days
Mortality 130 pts（4%）	Mortality 134 pts（4%）

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Findings

Physicians Survey

- ✓ 54% Dr experienced the discrepancy b/w intention and guided
- ✓ 74% Dr think it effective

Process

Usability

Drug	Before			After			Change -%
	Risk Meds	Appropriate dose	Appropriate rate	Risk Meds	Appropriate dose	Appropriate rate	
Antibiotic X	31	5	16.1	25	19	76.0	59.9
BPH Med	21	4	19.0	20	12	60.0	41.0
Anti-bleeding	24	0	0	21	8	38.1	38.1
Anticoagulant X	14	10	71.4	26	26	100.0	28.6
Total	410	269	65.6	442	370	83.7	18.1

Patients without renal DysFx	Before	After	P-value
Max Diff Cre, Med (IQR)	0.06 (0, 0.15)	0.06 (0, 0.14)	0.3
Diff Cre after Adm, Med (IQR)	0.02 (-0.01, 0.10)	0 (-0.03, 0.09)	0.0001
Incidence of renal DysFx （%）	50	46	0.01

Outcome

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Extension to Outpatients

- Extension of Decision Support System
  - Outpatients
  - Guided pharmacological therapy
    - Guided dose for drugs with renal adjustment
    - Guided labs for drugs with higher risk for ADE
  - Practice guide
    - Practice guideline of osteoporosis
- Prospective Cohort study
  - Outcome
    - Process
    - Patient outcomes

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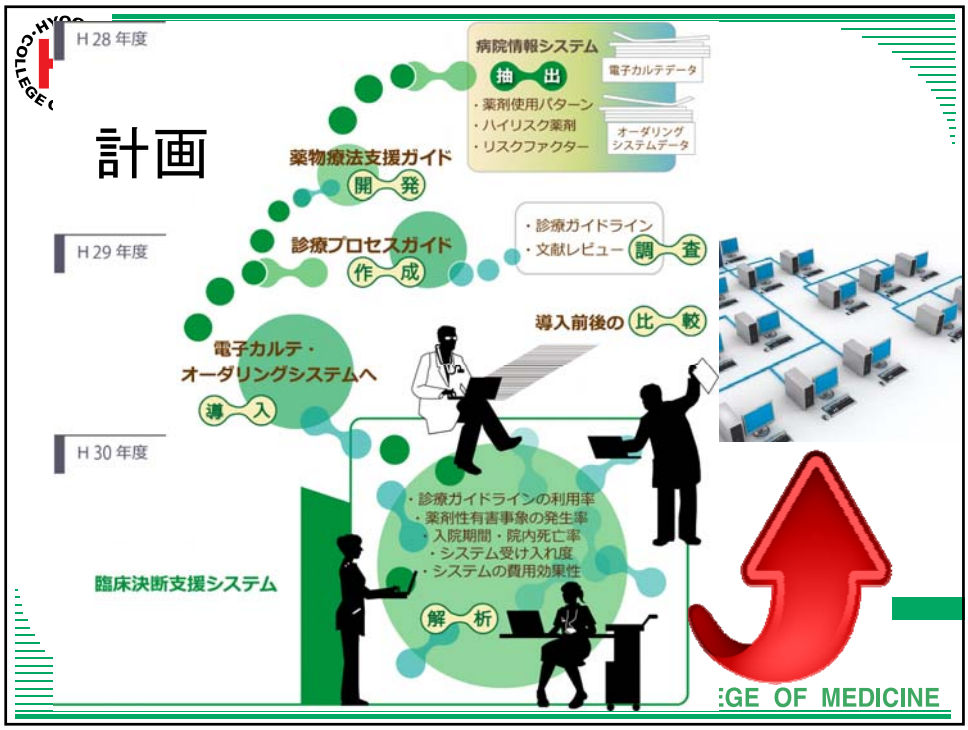
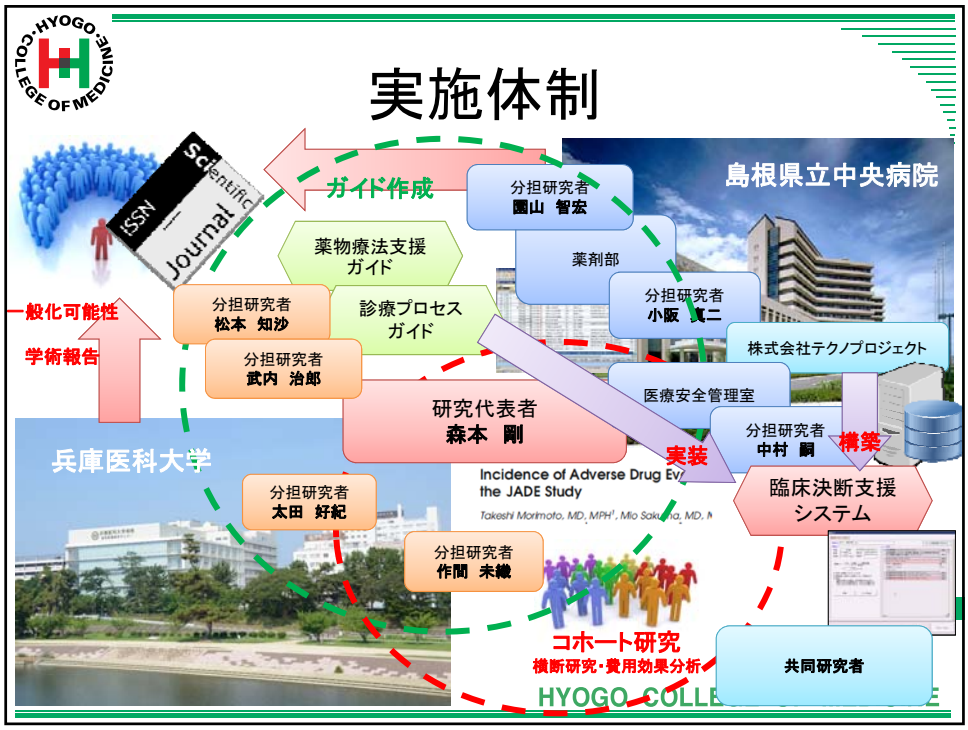

計画
H 28 年度
病院情報システム
抽出
電子カルテデータ
・薬剤使用パターン
・ハイリスク薬剤
・リスクファクター
オーダリングシステムデータ
薬物療法支援ガイド
開発
H 29 年度
診療プロセスガイド
作成
・診療ガイドライン
・文献レビュー
調査
導入前後の比較
電子カルテ・
オーダリングシステムへ
導入
H 30 年度
・診療ガイドラインの利用率
・薬剤性有害事象の発生率
・入院期間・院内死亡率
・システム受け入れ度
・システムの費用効果性
解析
臨床決断支援システム
EGE OF MEDICINE


実施体制
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Scientific
ISSN
Journal
ガイド作成
分担研究者
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島根県立中央病院
薬剤部
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ガイド
分担研究者
小阪 真二
株式会社テクノプロジェクト
一般化可能性
学術報告
分担研究者
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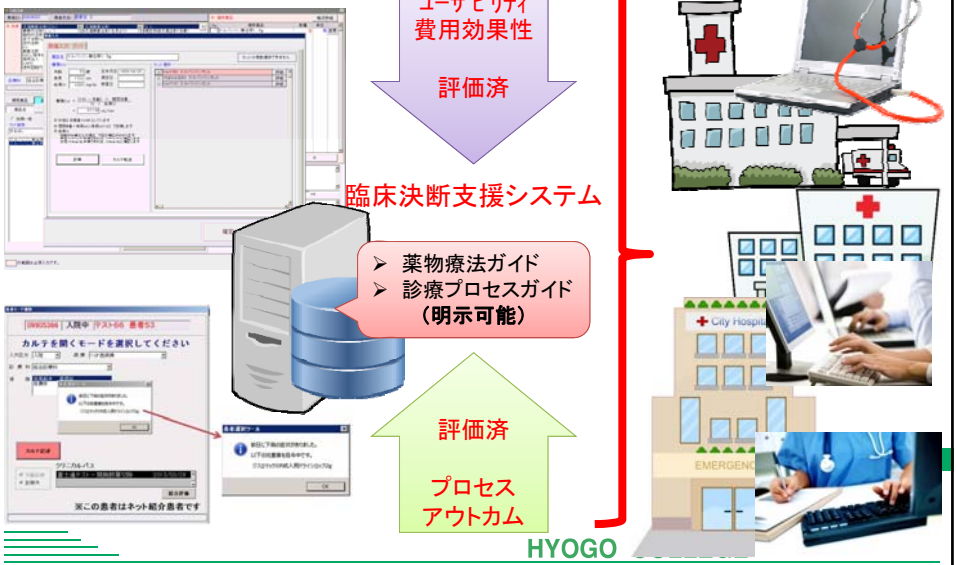
診療プロセス
ガイド
分担研究者
武内 治郎
医療安全管理室
研究代表者
森本 剛
分担研究者
中村 嗣
構築
実装
兵庫医科大学
Incidence of Adverse Drug Ev
the JADE Study
Takeshi Morimoto, MD, MPH1, Mio Sak
分担研究者
太田 好紀
臨床決断支援
システム
分担研究者
作間 未緒
コホート研究
横断研究・費用効果分析
共同研究者
HYOGO COLLE

最終成果物と一般化可能性



期待される効果

医療従事者	現在	臨床決断支援システム
医師	自己の知識に基づいて治療を決定	＋患者に適用される診療ガイドラインに基づいた治療が推奨され、改めて適否を判断
	患者の直近の状態や禁忌となる併存症を確認して、処方	＋患者の状態に応じた薬剤や用量が推奨され、改めて投与計画を判断
	電子カルテを網羅的にチェックして、対応の必要な状況を把握	＋対応の必要な状況が電子カルテ側から提供
薬剤師	相対的な禁忌薬剤や用量補正を徒手的にチェックして、処方医に連絡	機械的に判断できるチェック作業及び医師へ連絡はシステムが行い、その作業の監督とベッドサイドでのコミュニケーションに注力
看護師	看護記録の内容が医師に十分把握されない機会	対応の必要な状況が電子カルテ側から医師にリアルタイムで提供
パス作成チーム	新しいパスの作成ごとに、パスを構築し、関係者に周知	エビデンスに基づいたパスを組み込み、適応患者では自動的に提供

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Our Directions

No Computerized Support
All Potential ADEs Scrutinized
Comprehensive Collection
Manually Reviewed

Decision Support
Prespecified ADEs
Laboratory and Process
Automated Collection

Decision Support
All Potential ADEs
Comprehensive Collection
Automated Collection

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平成30年度厚生労働科学研究費補助金
政策科学総合研究事業
（臨床研究等ICT基盤構築・人工知能実装研究事業）

安全な薬物治療をリアルタイムで支援する臨床決断支援システムの開発に関する研究

導入された薬物療法支援ガイド- 腎機能

兵庫医科大学

太田好紀

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背景

CKD患者に対する不適切処方（inappropriate prescribing; IP）に関する過去の報告

- 23ヶ国、49研究
- IPの発生割合；入院で9%～81%、外来で13%～81%
- IPは病院滞在日数を延長（平均[標準偏差]：4.5[4.8]vs. 4.3[4.5]）、死亡率は40%上昇
- 研究は手動とコンピュータによるアラート機能が多かった（19研究/49研究）
- 最も多くIPを減少させたのは、医師のオーダー後速やかな薬剤師からの疑義照会
- 多種類の薬剤内服、既往歴、年齢がIPの予測因子

Int J Clin Pract 2017;71(7).

背景

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Int J Clin Pract 2017;71(7).

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目的

- 外来患者の薬剤処方時に、腎機能に応じた推奨投与量を表示することにより、適正処方数や薬剤師による疑義照会回数が変化するか検討する。その結果生じる、薬剤性有害事象への影響についても検討する

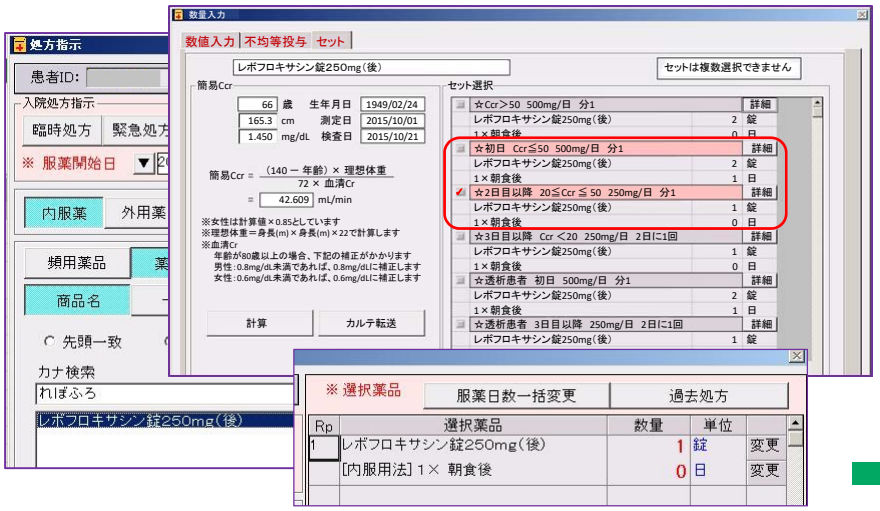
方法

- デザイン：前向きコホート研究

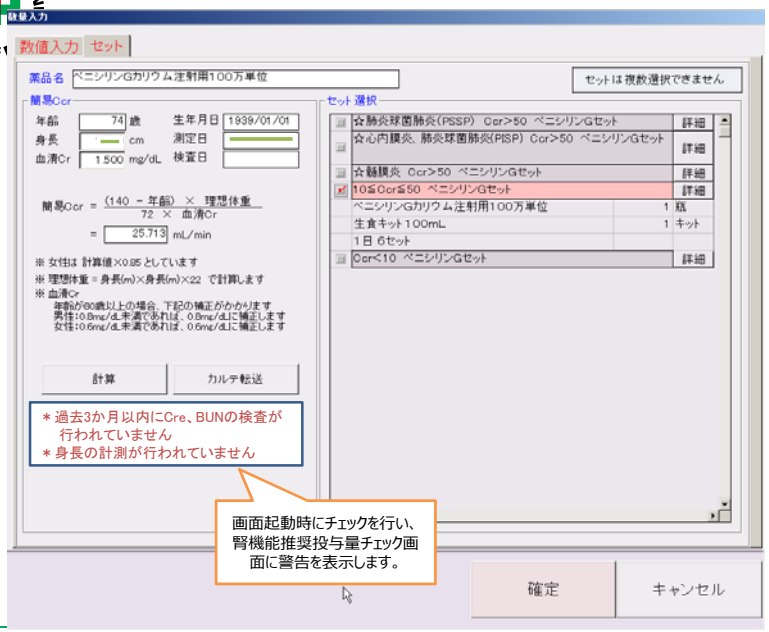
- 患者：18歳以上の外来通院患者
- 期間：「臨床決断支援システム（処方時の入力支援機能）」を導入時の前後各1年
  2017年10月～2018年9月：導入前
  2018年10月～2019年9月：導入後
- 対象画面：外来処方指示、救命救急処方指示、外来処置（注射専用）指示、外来処置（注射専用）カレンダー

処方時の入力支援機能の概要（導入前）

入院時処方入力支援機能の概要



外来処方入力支援機能の概要（追加機能）



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結果

- 「臨床決断支援システム」

導入前：2017年10月～2018年9月；1年

導入後：2018年10月～2018年12月；3ヶ月

全患者数: 9,926 人　　全処方数: 42,514 剤

導入前：患者数: 6,331 人　　処方数: 34,074 剤

導入後：患者数: 3,595 人　　処方数: 8,440 剤

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結果

- 「臨床決断支援システム」によるアラート人数
  - 導入前: 905 人 → 14.3%
  - 導入後: 350 人 → 9.7%
- eGFR＜60mL/分/1.73m²未満のアラート人数
  - 導入前: 461 人 → 23.3%
  - 導入後: 181 人 → 17.6%

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結果

- 「臨床決断支援システム」によるアラート数
  - 導入前: 2,522 剤 → 7.4%
  - 導入後: 511 剤 → 6.1%
- アラート後の処方変更数
  - 導入前: 15 剤 → 0.6%
  - 導入後: 45 剤 → 8.8%

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結果（導入後のアラート薬剤）

ファモチジン10mg	ザイザル錠	アロプリノール錠100mg
ファモチジン20mg	ザンタック錠150mg	エナラプリルM錠5
フロモックス	シプロキサン錠200mg	オロパタジン　5mg
ベザトールSR	シベノール錠100mg	ガスターD錠10mg
ベザフィブラート	ジャヌビア錠50mg	クラリスロマイシン錠200mg
ベネット錠17.5mg	セフカペンピボキシル100mg	グリクラジド錠20mg
ベネット錠2.5mg	セフジニルカプセル100mg	グリベンクラミド錠1.25mg
ホスミシン錠500mg	セフゾンカプセル100mg	グリミクロン20mg
メトグルコ250mg	セララ錠25mg	グリメピリド1mg
メトホルミン250mg	トラネキサム酸	グレースビット
ユナシン錠375mg	トランサミンカプセル250mg	ケフラックスカプセル
ユリーフ錠4mg	ネシーナ錠12.5mg	リマチル錠100mg
ラニチジン錠150mg	ネシーナ錠25mg	レニベース錠5
リカルボン錠1mg	バクタ配合顆粒	アマンタジン50mg
アマリール錠1mg	リセドロン酸17.5mg	アレロック50mg

延べ　511剤

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結果（処方変更有の薬剤）

ファモチジン10mg	ザイザル錠	アロプリノール錠100mg
ファモチジン20mg	ザンタック錠150mg	エナラプリルM錠5
フロモックス	シプロキサン錠200mg	オロパタジン　5mg
ベザトールSR	シベノール錠100mg	ガスターD錠10mg
ベザフィブラート	ジャヌビア錠50mg	クラリスロマイシン錠200mg
ベネット錠17.5mg	セフカペンピボキシル100mg	グリクラジド錠20mg
ベネット錠2.5mg	セフジニルカプセル100mg	グリベンクラミド錠1.25mg
ホスミシン錠500mg	セフゾンカプセル100mg	グリミクロン20mg
メトグルコ250mg	セララ錠25mg	グリメピリド1mg
メトホルミン250mg	トラネキサム酸	グレースビット
ユナシン錠375mg	トランサミンカプセル250mg	ケフラックスカプセル
ユリーフ錠4mg	ネシーナ錠12.5mg	リマチル錠100mg
ラニチジン錠150mg	ネシーナ錠25mg	レニベース錠5
リカルボン錠1mg	バクタ配合顆粒	アマンタジン50mg
アマリール錠1mg	リセドロン酸17.5mg	アレロック50mg

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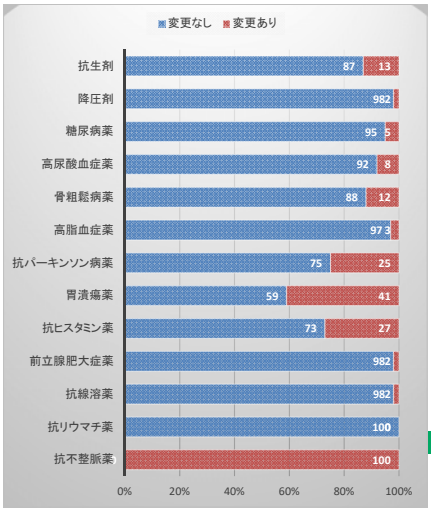
結果（処方変更有の薬剤）

	変更なし	変更あり
抗生剤	139	20
降圧剤	52	1
糖尿病薬	94	5
高尿酸血症薬	11	1
骨粗鬆病薬	14	2
高脂血症薬	37	1
抗パーキンソン病薬	3	1
胃潰瘍薬	10	7
抗ヒスタミン薬	11	4
前立腺肥大症薬	55	1
抗線溶薬	39	1
抗リウマチ薬	1	0
抗不整脈薬	0	1



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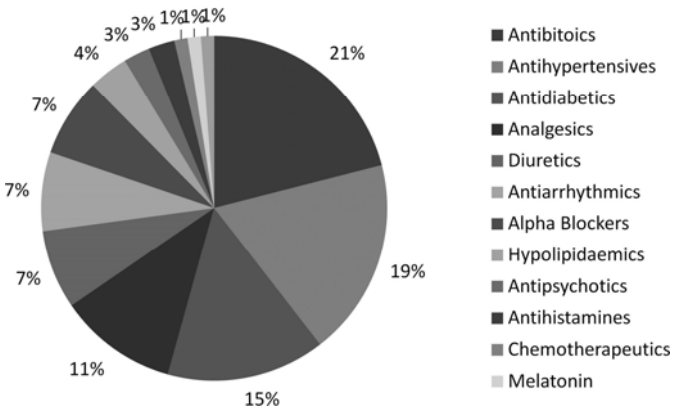
考察

The percentage distribution of PIMs amongst the prescriptions of elderly patients with CKD.



Postgrad Med J 2013;89:247-250

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平成30年度厚生労働科学研究費補助金
政策科学総合研究事業
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安全な薬物治療をリアルタイムで支援する臨床決断支援システムの開発に関する研究

導入された薬物療法ガイド

ー注意喚起対象薬剤

島根県立中央病院

園山　智宏

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研究の背景

- 添付文書は、医薬品ごとにその適正使用に関する注意喚起が記載されている公的文書である
- しかし、添付文書の情報量は多く、また、医薬品の製造販売後に新たに認められたリスク等をふまえて改訂がなされることから、医療従事者が常に最新の添付文書の内容を薬剤ごとに理解・把握することは困難である

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本研究の概要

- 本研究は、添付文書の記載要領の中でも、薬剤投与中に見落としがちな投与期間中の定期的な検査に関する注意喚起に着目し、臨床決断支援システムに組み込まれた注意喚起の影響を評価しようとするものである

過去の研究との比較(1)

- 添付文書に定期的な検査の必要性が記載されている薬剤について、処方後に検査実施の有無を薬剤部にてシステム的に抽出し、医師へ検査追加の提案や疑義照会を行っているとの報告は散見される(中村敏明ら、医療薬学39(4), 199-207, 2013　他)
- しかし、処方後のチェックであるため、外来患者においては対応が遅れる可能性がある

過去の研究との比較（2）

- また、がん化学療法におけるB型肝炎ウイルス再活性化対策として、過去のHBV関連検査の有無を電子カルテ上の抗がん薬オーダー時にチェックし、アラートを出すことで検査実施率が向上したとの報告がある（高口ら、日本消化器病学会雑誌（suppl-2）114, 482, 2017）
- ただし、この機能はB型肝炎関連の検査項目と抗がん薬の組み合わせに特化したものである

過去の研究との比較（3）

- 今回の研究は、医師の処方時に過去の検査実施の有無をシステムで確認し、注意喚起を行うものであり、かつ、薬剤と検査値の組み合わせやコメントの内容がマスタで自由に設定できるため、汎用性がある点で従来の研究とは異なる
- また、外来診療においては処方医以外のスタッフがチェックを行う機会は限定されているため、処方時にシステム的な注意喚起を行うことは特に有益である可能性がある

本研究の概要

- 具体的には、次ページ以降に示す９種類の薬剤について、過去の検査期日を元に検査の必要性をシステムで自動判断し、医師の処方時に注意喚起を行う機能を電子カルテ上に搭載し、システム導入前後での検査の実施状況を検討した

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対象薬剤

1. 眼障害に対する注意喚起
   - アミオダロン塩酸塩
2. 甲状腺機能障害に対する注意喚起
   - ニボルマブ、ペムブロリズマブ、アテゾリズマブ、パゾパニブ塩酸塩、レゴラフェニブ、アキシチニブ、スニチニブリンゴ酸塩
3. 肝機能障害に対する注意喚起
   - ビルダグリプチン

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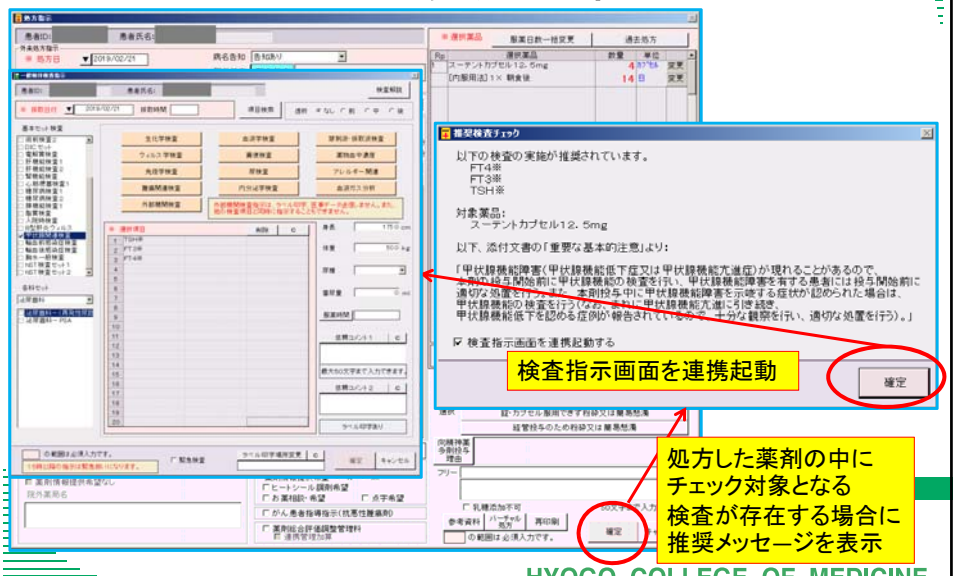
処方→注意喚起→検査指示



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アラートに対する対応状況

1. 眼障害(アミオダロン塩酸塩速崩錠100mg):患者数

	全患者数	アミオダロン処方患者数	(潜在)アラートあり c)	対応検査あり d), e)
Pre a)	37,093	72(0.19%)	64(88.9%)	3(4.7%)
Post b)	20,642	54(0.26%)	45(83.3%)	2(4.2%)

a) システム導入前(2017/10/1-2018/9/30の1年間)
b) システム導入後(2018/10/1-2019/1/31の3ヶ月)
c) アミオダロン処方患者数に対する割合
d) 処方後3ヶ月以内に対応する検査が行われた件数
e) (潜在)アラートありに対する割合

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アラートに対する対応状況

1. 眼障害（アミオダロン塩酸塩速崩錠100mg）：処方数

	アミオダロン処方数	（潜在）アラートあり c)	対応検査あり d), e)
Pre a)	451	389(86.3%)	10(2.6%)
Post b)	111	87(78.4%)	3(3.4%)

a) システム導入前（2017/10/1-2018/9/30の1年間）
b) システム導入後（2018/10/1-2019/1/31の3ヶ月）
c) アミオダロン処方数に対する割合
d) 処方後3ヶ月以内に対応する検査が行われた件数
e) （潜在）アラートありに対する割合

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アラートに対する対応状況

2. 甲状腺機能障害（スチバーガ錠40mg）：患者数

	全患者数	スチバーガ処方患者数	（潜在）アラートあり c)	対応検査あり d), e)
Pre a)	37,093	20(0.05%)	11(55.0%)	7(63.6%)
Post b)	20,642	13(0.06%)	2(15.4%)	1(50.0%)

a) システム導入前（2017/10/1-2018/9/30の1年間）
b) システム導入後（2018/10/1-2019/1/31の3ヶ月）
c) スチバーガ処方患者数に対する割合
d) 処方後3ヶ月以内に対応する検査が行われた件数
e) （潜在）アラートありに対する割合

HYOGO COLLEGE OF MEDICINE

アラートに対する対応状況

2. 甲状腺機能障害（スチバーガ錠40mg）：処方数

	スチバーガ処方数	（潜在）アラートあり c)	対応検査あり d), e)
Pre a)	64	38(59.4%)	11(28.9%)
Post b)	12	3(25.0%)	2(66.7%)

a) システム導入前（2017/10/1-2018/9/30の1年間）
b) システム導入後（2018/10/1-2019/1/31の3ヶ月）
c) スチバーガ処方数に対する割合
d) 処方後3ヶ月以内に対応する検査が行われた件数
e) （潜在）アラートありに対する割合

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アラートに対する対応状況

3. 肝機能障害（エクア錠50mg）：患者数

	全患者数	エクア処方患者数	（潜在）アラートあり c)	対応検査あり d), e)
Pre a)	37,093	330(0.89%)	155(47.0%)	44(28.4%)
Post b)	20,642	244(1.18%)	104(42.6%)	13(12.5%)

a) システム導入前（2017/10/1-2018/9/30の1年間）
b) システム導入後（2018/10/1-2019/1/31の3ヶ月）
c) エクア処方患者数に対する割合
d) 処方後3ヶ月以内に対応する検査が行われた件数
e) （潜在）アラートありに対する割合

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アラートに対する対応状況

3. 肝機能障害（エクア錠50mg）：処方数

	エクア処方数	（潜在）アラートあり c)	対応検査あり d), e)
Pre a)	1,701	643(37.8%)	77(12.0%)
Post b)	452	149(33.0%)	15(10.1%)

a) システム導入前（2017/10/1-2018/9/30の1年間）
b) システム導入後（2018/10/1-2019/1/31の3ヶ月）
c) エクア処方数に対する割合
d) 処方後3ヶ月以内に対応する検査が行われた件数
e) （潜在）アラートありに対する割合

結語

- 投与期間中の定期的な検査が必要な薬剤に対して、検査の必要性をシステムで自動判断し、医師の処方時に注意喚起を行う臨床決断支援システムを導入した
- システム導入後の検査状況に関して今後も調査を継続し、本システムにより検査実施率が向上することで、薬剤による有害事象が防止または緩和されるかの比較・検討を行う予定である

平成30年度厚生労働科学研究費補助金
政策科学総合研究事業
（臨床研究等ICT基盤構築・人工知能実装研究事業）

安全な薬物治療をリアルタイムで支援する臨床決断支援システムの開発に関する研究

導入された診療プロセスガイド

島根県立中央病院 感染症科

中村 嗣

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背景

- 高齢化に伴い本邦の骨粗鬆症患者は増加
  - 骨粗鬆症有病者：約1,300万人
  - 大腿骨近位部骨折：18万人/年
  - 超過死亡：27,000人
  - 身体機能の低下：75,000人 *（診断と治療 2016）*
- 骨粗鬆症は予防医療・治療が重要
- 骨粗鬆症ガイドライン（日本骨粗鬆症学会、2015）
  - IT環境の不備がガイドライン活用の阻害要因 *（厚生労働省委託事業 2016）*
  - 骨粗鬆症治療が行われている患者：約4～20%
  - 治療開始後1年での服薬順守率：50%程度と推定 *（臨床整形外科 2016）*
  - ステロイド性骨粗鬆症も、診療内容は不明
  - 欧米では予防医療推進で、再骨折率・死亡率・医療費の低下 *（Osteoporos Int. 2011）*
- ビスホスホネート製剤
  - 骨粗鬆症治療の第一選択薬の一つ
  - 重大な副作用もあり、適切な管理が必要

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目的

- 臨床現場でのガイドラインの遵守率
- 電子カルテシステムは有用か
  - 統合情報システム（IIMS：電子カルテシステム）で介入することが臨床決断を支援するか
  - 介入前後でのガイドラインの推奨医療実施率をみることで、実施率が増加するか
  - 複雑なガイドラインをアラート+オーダー支援

目的

- 介入前後でのガイドラインの推奨医療実施率
  - 原発性骨粗鬆症
    - 骨密度測定
    - ビスホスホネート処方開始時の検査
  - ステロイド性骨粗鬆症
    - ビスホスホネート処方を推奨の場合
    - 骨折歴の確認を推奨の場合
    - 骨密度測定を推奨の場合

方法

- 骨粗鬆症ガイドライン2015の内容を、島根県立中央病院統合情報システム（IIMS）に実装
- ベースラインデータ（介入前）として、1年（2017年10月～2018年9月）のデータをアラートメッセージを表示せずに取得
- アラートメッセージを表示（介入後）した導入後3ヶ月（2018年10月～12月）のデータを取得
- 介入前 vs 介入後で、ガイドライン内容の遵守割合を比較する

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原発性骨粗鬆症

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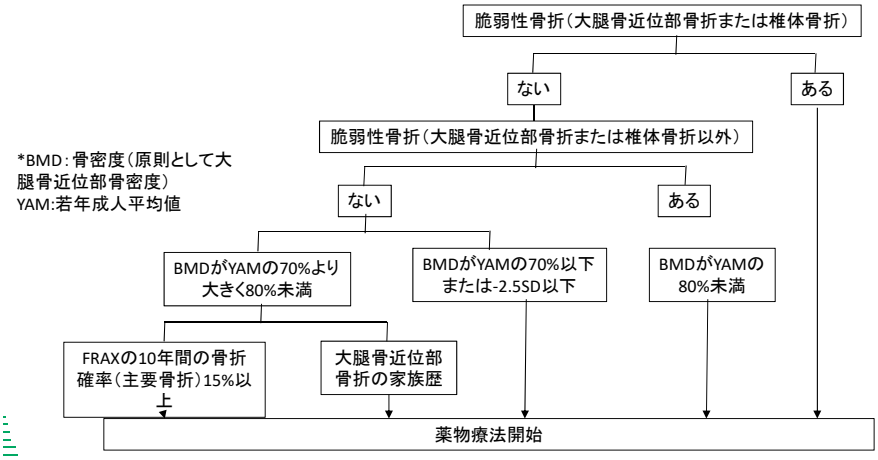
原発性骨粗鬆症の薬物療法開始基準



*BMD：骨密度（原則として大腿骨近位部骨密度）
YAM:若年成人平均値

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ガイドラインに基づく臨床支援決断システムⅠ
＜原発性骨粗鬆症＞

対象：原発性骨粗鬆症又は骨粗鬆症の病名を有する患者
骨粗鬆症診療ガイドライン2015に基づき以下の予防医療喚起を行う

A. 過去１年以内に骨密度検査がない場合
→　骨密度検査を推奨

B. ビスホスホネート初回投与時*
→過去3か月以内に血清Ca, P, Mg, Cre, BUN及び骨密度検査が無い場合には同検査を推奨

過去三か月に同処方のない者

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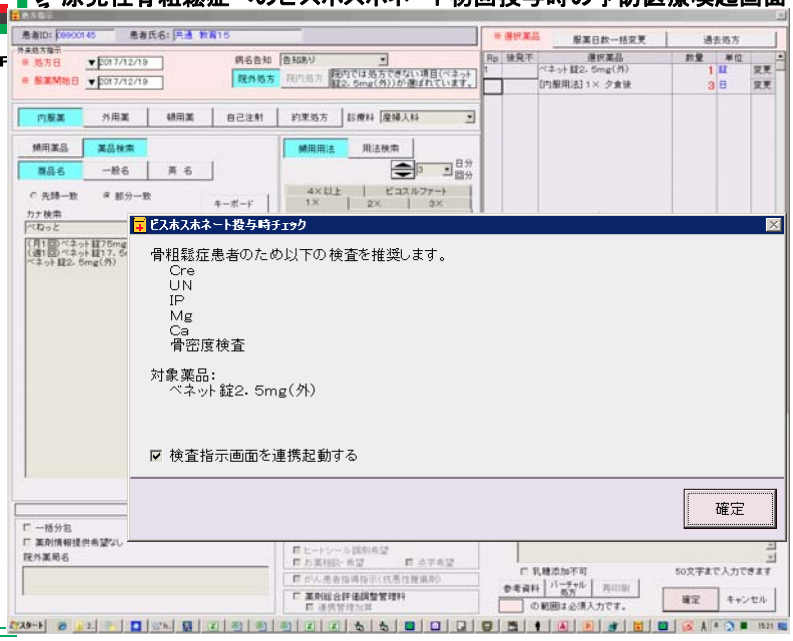
原発性骨粗鬆症へのビスホスホネート初回投与時の予防医療喚起画面



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結果（2017/10/1-2018/12/31）

項目	all (n=2,811) n (%) or meanssd
介入後	629 (22)
内科系診療科	1,883 (68)
診療科詳細	
血液腫瘍科	255 (9.07)
循環器科	76 (2.70)
内分泌代謝科	8 (0.28)
消化器科	99 (10.64)
総合診療科	424 (15.08)
肝臓内科	20 (0.71)
神経内科	163 (5.80)
リウマチ・アレルギー科	564 (20.06)
呼吸器科	74 (2.63)
心臓血管外科	18 (0.64)
皮膚科	30 (1.07)
産婦人科	38 (1.35)
腎臓科	142 (5.05)
乳腺科	58 (9.18)
脳神経外科	2 (0.07)
整形外科	396 (14.09)
耳鼻咽喉科	8 (0.28)
呼吸器外科	9 (0.32)
外科	4 (0.14)
薬剤局	23 (0.82)
医師経験年数	23±9
骨粗鬆症患者	2,650 (94)
骨粗鬆症患者の骨密度検査アラート	
対象外	161 (5.73)
なし	711 (25.29)
あり	1,939 (68.98)
ビスホスホネート初回投与	196 (7.0)
ビスホスホネート初回投与時アラート	
対象外	2,615 (93.03)
なし	11 (0.39)
あり	185 (6.58)
骨粗鬆症患者の検査有無	
対象外	872 (31.02)
なし	1,833 (65.21)
あり	106 (3.77)
ビスホスホネート初回投与時骨塩定量	
対象外	2,626 (93.42)
なし	142 (5.05)
あり	43 (1.53)
ビスホスホネート初回投与時血液検査	
対象外	2,626 (93.42)
なし	163 (5.80)
あり	22 (0.78)
ビスホスホネート初回投与時検査有無	
対象外	2,626 (93.42)
なし	176 (6.26)
あり	9 (0.32)

処方数：2,811 （総外来患者数：57,735）
介入後 629（22%）
処方医師経験年数：23±9
内科系診療科：1,883（68%）
骨粗鬆症患者：2,650（94%）
骨密度検査アラート：1,939（69%）
検査実施：106（3.8%）
ビスホスホネート初回投与者：196(7.0%)
初回投与時アラート：185/196（94%）
骨塩定量アラート：43/196（22%）
血液検査アラート：22/196（11%）
その他検査：9/196（4.6%）

内科系診療科：総合診療科、循環器科、消化器科、肝臓内科、呼吸器科、神経内科、リウマチ・アレルギー科、内分泌代謝科、血液腫瘍科

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結果

（2017/10/1-2018/9/30 vs 2018/10/1-2018/12/31）

	介入前 (n=2,182)	介入後 (n=629)	
項目	no(%) or mean ± sd		*p*-value
内科系診療科	1,476 (68)	40 (65)	0.161
医師経験年数	23±9	23±8	0.5808
骨粗鬆症患者	2,077 (95)	573 (91)	0.000 *
骨粗鬆症患者の骨密度検査アラート			0.000 *
対象外	105 (4.81)	56 (8.90)	
なし	491 (22.50)	220 (34.98)	
あり	1,586 (72.69)	353 (56.12)	
ビスホスホネート初回投与	136 (6.2)	60 (9.5)	0.004 *
ビスホスホネート初回投与時アラート			0.002 *
対象外	2,046 (93.77)	569 (90.46)	
なし	5 (0.23)	6 (0.95)	
あり	131 (6.00)	54 (8.59)	
骨粗鬆症患者の検査有無			0.000 *
対象外	596 (27.31)	276 (43.88)	
なし	1,518 (69.57)	315 (50.08)	
あり	68 (3.12)	38 (6.04)	
ビスホスホネート初回投与時骨塩定量			0.002 *
対象外	2,051 (94.00)	575 (91.41)	
なし	107 (4.90)	35 (5.56)	
あり	24 (1.10)	19 (3.02)	
ビスホスホネート初回投与時血液検査			0.000 *
対象外	2,051 (94.00)	575 (91.41)	
なし	129 (5.91)	34 (5.41)	
あり	2 (0.09)	20 (3.18)	
ビスホスホネート初回投与時検査有無			0.000 *
対象外	2,051 (94.00)	575 (91.41)	
なし	131 (6.00)	45 (7.15)	
あり	0 (0.00)	9 (1.43)	

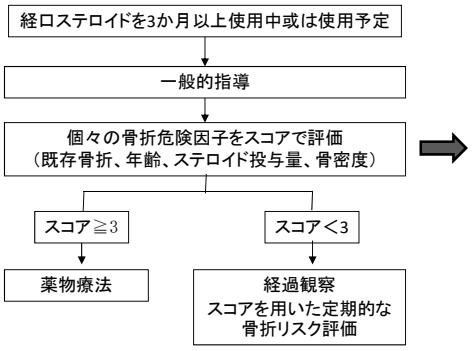
介入前（2,182）vs 介入後（629）

診療科・医師経験年数：差なし
骨粗鬆症患者は介入前が多かった

骨密度検査アラート：減少
検査実施：増加
ﾋﾞｽﾎｽﾎﾈｰﾄ初回投与者：増加
　初回投与時アラート：増加
　骨塩定量：増加
　血液検査：増加
　その他検査：増加

ステロイド性骨粗鬆症

ステロイド性骨粗鬆症の薬物療法開始基準



危険因子		スコア
既存骨折	なし	0
	あり	7
年齢（歳）	＜50	0
	50≦ ＜65	2
	≧65	4
ステロイド投与量（PSL換算mg/日）	＜5	0
	5≦ ＜7.5	1
	≧7.5	4
腰椎骨密度（%YAM）	≧80	0
	70≦ ＜80	2
	＜70	4

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ガイドラインに基づく臨床支援決断システムⅡ ＜ステロイド性骨粗鬆症＞

対象：経口ステロイドを3か月以上使用中の外来患者

骨粗鬆症診療ガイドライン2015に基づき以下の予防医療喚起を行う

A. ステロイド性骨粗鬆症の薬物療法開始基準1-6に該当する場合

→ビスホスホネート処方を推奨

B. ステロイド性骨粗鬆症の薬物療法開始基準に該当しない場合

→骨折歴を確認を推奨

C. 過去一年間骨密度測定が実施されていない場合

→骨密度測定を推奨

危険因子		スコア
既存骨折	なし	0
	あり	7
年齢（歳）	＜50	0
	50≦ ＜65	2
	≧65	4
ステロイド投与量（PSL換算mg/日）	＜5	0
	5≦ ＜7.5	1
	≧7.5	4
腰椎骨密度（%YAM）	≧80	0
	70≦ ＜80	2
	＜70	4

*ステロイド性骨粗鬆症の薬物療法開始基準**

1. ステロイド投与量（PSL換算）7.5mg/日以上
2. 65歳以上
3. 50歳以上＆ステロイド投与量（PSL換算）5mg/日以上
4. 骨密度†70%以下
5. 骨密度† 70～80%＆ステロイド投与量5.0mg/日以上
6. 骨密度† 70～80%＆50歳以上

*対象：経口ステロイド3か月以上使用中の患者
† 一年以内かつ直近の骨密度

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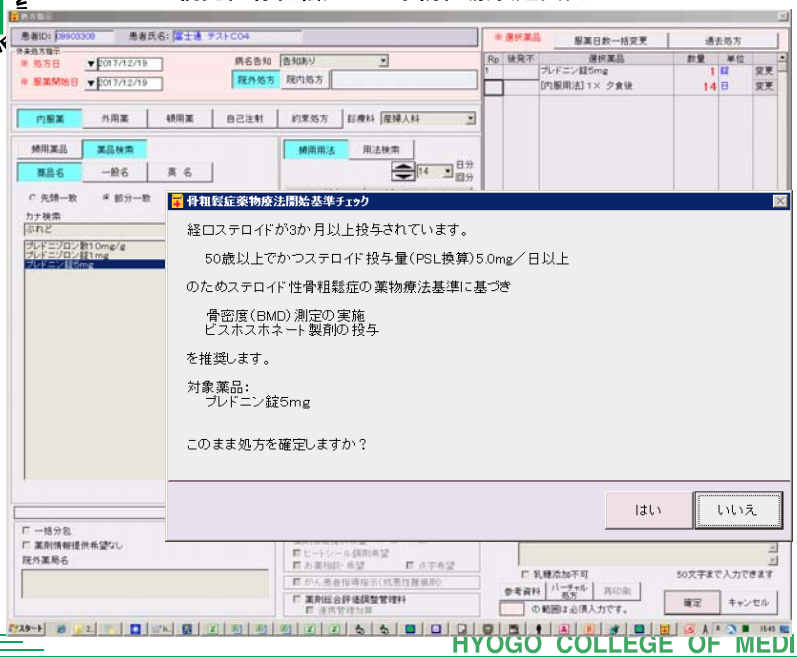
続発性骨粗鬆症への予防医療喚起画面



結果(2017/10/1-2018/12/31)

項目	All (n=6,930) n (%) or mean±sd
介入後	1,469 (21)
内科系診療科	4,578 (67)
診療科詳細	
血液腫瘍科	911 (13.15)
循環器科	63 (0.91)
臨床腫瘍科	5 (0.07)
内分泌代謝科	209 (3.02)
消化器科	625 (9.02)
総合診療科	778 (11.23)
感染症科	1 (0.01)
肝臓内科	46 (0.66)
神経内科	351 (5.06)
リウマチ・アレルギー科	933 (13.46)
呼吸器科	656 (9.47)
心臓血管外科	9 (0.13)
皮膚科	146 (2.11)
救命救急科	27 (0.39)
産婦人科	7 (0.10)
集中治療科	1 (0.01)
形成外科	3 (0.04)
腎臓科	398 (5.74)
膵科	22 (0.32)
乳腺科	228 (3.29)
新生児科	30 (0.43)
脳神経外科	56 (0.81)
整形外科	33 (0.48)
耳鼻咽喉科	169 (2.44)
小児科	516 (7.45)
放射線科	1 (0.01)
呼吸器外科	245 (3.54)
歯科口腔外科	2 (0.03)
外科	225 (3.25)
泌尿器科	160 (2.31)
薬剤局	73 (1.05)
その他	1 (0.01)
アラート理由	
服薬なし	2,916 (42.08)
PSL換算 7.5mg以上	307 (4.43)
50歳以上＆PSL換算5mg以上	522 (7.53)
65歳以上	3,117 (44.98)
骨密度70%以下	53 (0.76)
骨密度70-80%＆PSL換算5.0mg以上	11 (0.16)
骨密度70-80%＆50歳以上	4 (0.06)
服薬状態年数	23±9
3か月以上のステロイド連用	4,791 (69)
ビスホスホネート処方推奨有無	
対象外	2,916 (42.08)
なし	1,773 (25.58)
あり	2,241 (32.34)
骨折歴確認推奨有無	
対象外	6,153 (88.79)
なし	0 (0.0)
あり	777 (11.21)
骨密度測定推奨有無	
対象外	2,139 (30.87)
なし	686 (9.90)
あり	4,105 (59.24)
ビスホスホネート処方実施有無	
対象外	4,689 (67.66)
なし	2,126 (30.68)
あり	115 (1.66)
骨密度測定実施有無	
対象外	2,825 (40.76)
なし	3,882 (56.02)
あり	223 (3.22)

処方数:6,930 （総外来患者数:57,735）
　介入後:1,469（21%）
処方医師経験年数:23±9
内科系診療科:4,578（67%）
アラート理由
　65歳以上が多かった:3,117（45%）
　3か月以上のステロイド連用:4,791 (69%)
ビスホスホネート処方推奨:2,241（32%）
骨折歴確認推奨:777（11%）
骨密度測定推奨:4,105（59%）
ビスホスホネート処方実施:115（1.7%）
骨密度測定実施:223（3.2%）

内科系診療科:総合診療科、感染症科、循環器科、消化器科、肝臓内科、呼吸器科、神経内科、リウマチ・アレルギー科、内分泌代謝科、血液腫瘍科、臨床腫瘍科

結果

（2017/10/1-2018/9/30 vs 2018/10/1-2018/12/31）

	介入前 (n=5,461)	介入後 (n=1,469)	
項目	n (%) or mean ± sd		p-value
内科系診療科	3,634 (67)	944 (65)	0.109
アラート理由			0.129
該当なし	2,338 (42.81)	578 (39.35)	
PSL換算 7.5mg以上	245 (4.49)	62 (4.22)	
50歳以上＆PSL換算5mg以上	410 (7.51)	112 (7.62)	
65歳以上	2,418 (44.28)	699 (47.58)	
骨密度70%以下	41 (0.75)	12 (0.82)	
骨密度70-80%＆PSL換算5.0mg以上	7 (0.13)	4 (0.27)	
骨密度70-80%＆50歳以上	2 (0.04)	2 (0.14)	
医師経験年数	23±9	23±9	0.3129
3か月以上のステロイド連用	3,752 (69)	1,039 (71)	0.136
ビスホスホネート処方推奨有無			0.018 *
対象外	2,338 (42.81)	578 (39.35)	
なし	1,360 (24.90)	413 (28.11)	
あり	1,763 (32.28)	478 (32.54)	
骨折歴確認推奨有無			0.12
対象外	4,832 (88.28)	1,321 (89.93)	
なし	0 (0.00)	0 (0.00)	
あり	629 (11.52)	14 (10.07)	
骨密度測定推奨有無			0.000 *
対象外	1,709 (31.29)	430 (29.27)	
なし	413 (7.56)	273 (18.58)	
あり	3,339 (61.14)	766 (52.14)	
ビスホスホネート処方実施有無			0.137
対象外	3,698 (67.72)	991 (67.46)	
なし	1,681 (30.78)	445 (30.29)	
あり	82 (1.50)	33 (2.25)	
骨密度測定実施有無			0.000 *
対象外	2,122 (38.86)	703 (47.86)	
なし	3,207 (58.73)	675 (45.95)	
あり	132 (2.42)	91 (6.19)	

診療科・アラート理由：不変
医師経験年数：不変
ステロイド使用量：不変
ビスホスホネート処方推奨
　「あり」不変 「なし」増加
骨折歴確認推奨：不変
骨密度測定推奨
　「あり」減少 「なし」増加
ビスホスホネート処方実施：不変
骨密度測定実施：増加した

考察

【原発性骨粗鬆症】

- 介入により検査、投薬共に増加した

【ステロイド骨粗鬆症】

- 介入でビスホスホネート処方は増加しなかったが、骨密度検査は増加した

- 検査の推奨は従うが、処方の推奨に関しては他の事項を検討して慎重に行っている可能性がある

文献

- IT環境の整備は重要
  - IT環境は、病院によりばらつきが大きく、EBMや診療ガイドライン活用の阻害要因となっている

平成26-27 年度厚生労働省委託事業：EBM (根拠に基づく医療)普及推進事業
http://minds4.jcqhc.or.jp/implementation/qip/pdf/report_h26-27.pdf

- 検査のガイドライン遵守率は、公表されると件数は増加はするものの十分ではない
  - The frequency of testing increased from 2.5% to 3.6% during the study period ($p < 0.001$). *（J Sex Med. 2015）*
- 手術のガイドラインは守られやすい
  - very high compliance rates (>90%) for every ERAS guideline. *（World J Surg. 2017）*

結語

- ガイドラインの推奨を反映した診療を行う上で、臨床決断支援システムは有用である

平成30年度厚生労働科学研究費補助金
政策科学総合研究事業
（臨床研究等ICT基盤構築・人工知能実装研究事業）

安全な薬物治療をリアルタイムで支援する臨床決断支援システムの開発に関する研究

導入前後のコホート研究データ

兵庫医科大学　臨床疫学

作間　未織

HYOGO COLLEGE OF MEDICINE

目　　的

システム導入前の1年間（2017年10月1日-2018年9月30日）と導入後の3か月間（2018年10月1日-2018年12月31日）における、患者背景や臨床データの推移、臨床決断支援システム稼働状況について報告する

HYOGO COLLEGE OF MEDICINE

患者背景

変数	導入前 (N=37,093)	導入後 (N=20,642)
年齢 （中央値、四分位）	57 (34, 72)	60 (39, 73)
65歳以上, n (%)	14,439 (39)	8,934 (43)
男性, n (%)	16,370 (44)	9,286 (45)
外来受診数 （中央値、四分位）	4 (2, 7)	2 (1, 3)
入院歴, n (%)	7,827 (21)	2,222(11)
喫煙歴, n (%)		
喫煙なし	17,485 (47)	10,037 (49)
過去喫煙	6,258 (17)	4,079 (20)
現喫煙	3,189 (9)	1,844 (9)
不明	10,161 (27)	4,682 (23)
既往歴, n (%)	15,265 (41)	9,911 (48)
家族歴, n (%)	1,411 (3.8)	917 (4.4)

HYOGO COLLEGE OF MEDICINE

現在の状況

- 稼働中の決断支援システム:

(1) 腎機能に応じた薬剤の推奨投与に関する支援
(2) 医薬品添付文書上の定期検査に関する支援
(3) 骨粗鬆症ガイドラインに基づく支援－原発性骨粗鬆症
(4) 骨粗鬆症ガイドラインに基づく支援—ステロイド性骨粗鬆症

- 導入前1年間に外来受診した患者総数: 37,093名
- 導入前1年間の延べ外来受診数: 209,522名

- 導入後3か月間に外来受診した患者総数: 20,642名
- 導入後3か月間の延べ外来受診数: 52,987名

HYOGO COLLEGE OF MEDICINE

患者背景とアラート稼働状況

HYOGO COLLEGE OF MEDICINE

薬物療法支援ガイド―腎機能

HYOGO COLLEGE OF MEDICINE

腎機能別推奨投与アラート

- アラート対象処方を受けた患者数:
  導入前　6,331人 (17%)
  導入後　3,595人 (17%)
- アラートを受けた患者数:
  導入前　905人 (14%)
  導入後　350人 (9%)
- アラート対象処方を受けた患者の該当薬剤処方回数
  （中央値、最小、最大）:
  導入前　3件 (1, 78)
  導入後　2件 (1, 24)
- アラート対象処方を受けた患者のアラート回数
  （中央値、最小、最大）:
  導入前　0件 (0, 22)
  導入後　0件 (0, 8)

HYOGO COLLEGE OF MEDICINE

腎機能別推奨投与アラート

- アラート対象処方数:
  導入前　34,074件
  導入後　8,440件
- アラート稼働回数:
  導入前　2,552件 (7%)
  導入後　511件 (6%)
- 推奨投与への変更を行った回数:
  導入前　15件 (0.6%)
  導入後　45件 (9%)

HYOGO COLLEGE OF MEDICINE

BUN (mg/dl) 値の推移

変数	導入前 (N=37,093)	導入後 (N=20,642)
アラート対象薬剤を投与された患者数, n(%)	6,331 (17)	3,595 (17)
最大値 （中央値、四分位）	18.3 (14.3, 23.9)	17.5 (14, 22.6)
最小値	12.4 (9.6, 15.7)	15.3 (11.9, 19.1)
期間最初値	15.1 (12.1, 19.2)	16.4 (13, 20.7)
期間最終値	15.2 (12, 19.5)	16.3 (13.1, 21)
変化量（最大一最小）	5.3 (1.9, 10)	0.7 (0, 4.4)
変化量（最終一最初）	0 (−0.9, 2.7)	0 (0, 1)
アラート対象薬剤の投与がない患者数, n(%)	30,762 (83)	17,047 (83)
最大値	15.1 (11.8, 19.4)	15.1 (12, 19.3)
最小値	12.2 (9.2, 15.5)	13.5 (10.5, 17.2)
期間最初値	13.8 (10.8, 17.5)	14.4 (11.4, 18.4)
期間最終値	13.6 (10.6, 17.3)	14.3 (11.3, 18.1)
変化量（最大一最小）	1.3 (0, 5.7)	0 (0, 2.6)
変化量（最終一最初）	0 (0, 0.6)	0 (0, 0)

Cr (mg/dl) 値の推移

変数	導入前 (N=37,093)	導入後 (N=20,642)
アラート対象薬剤を投与された患者数, n(%)	6,331 (17)	3,595 (17)
最大値　最大値 （中央値、四分位）	0.8 (0.7, 1.1)	0.8 (0.7, 1.1)
最小値	0.7 (0.6, 0.9)	0.8 (0.6, 1.0)
期間最初値	0.8 (0.6, 0.9)	0.8 (0.7, 1)
期間最終値	0.8 (0.6, 0.9)	0.8 (0.7, 1.0)
変化量（最大一最小）	0.1 (0.04, 0.2)	0.02 (0, 0.1)
変化量（最終一最初）	0 (−0.03, 0.06)	0 (0, 0.03)
アラート対象薬剤の投与がない患者数, n(%)	30,762 (83)	17,047 (83)
最大値	0.7 (0.6, 0.9)	0.7 (0.6, 0.9)
最小値	0.6 (0.5, 0.8)	0.7 (0.5, 0.8)
期間最初値	0.7 (0.5, 0.8)	0.7 (0.6, 0.9)
期間最終値	0.7 (0.5, 0.8)	0.7 (0.6, 0.9)
変化量（最大一最小）	0.03 (0, 0.1)	0 (0, 0.05)
変化量（最終一最初）	0 (0, 0.02)	0 (0, 0)

EGFR (ml/分/1.73m^2) 値の推移

変数	導入前 (N=37,093)	導入後 (N=20,642)
アラート対象薬剤を投与された患者数, n(%)	6,331 (17)	3,595 (17)
最大値　最大値　(中央値、四分位)	79.4 (63.2, 96.7)	70.6 (55.6, 86.7)
最小値	65.7 (49.8, 81.2)	65.7 (50.7, 80.6)
期間最初値	72.8 (56.8, 88.7)	68.3 (53.5, 83.8)
期間最終値	71.9 (56.2, 87.8)	67.7 (52.8, 83.2)
変化量(最大一最小)	10.9 (3.9, 20.2)	1.4 (0, 8.0)
変化量(最終一最初)	0 (−3.6, 4.3)	0 (0, 0)
アラート対象薬剤の投与がない患者数, n(%)	30,762 (83)	17,047 (83)
最大値	83 (66, 103)	79 (62, 97)
最小値	75 (58, 93)	74 (58, 92)
期間最初値	79 (62, 98)	76 (60, 94)
期間最終値	79 (62, 97)	76 (60, 94)
変化量(最大一最小)	2.3 (0, 13.0)	0 (0, 4.8)
変化量(最終一最初)	0 (0, 1.0)	0 (0, 0)

薬物療法支援ガイド一定期検査推奨薬剤

HYOGO COLLEGE OF MEDICINE

定期検査推奨薬剤

注意喚起	薬剤名	対象検査項目
肝機能障害	エクア錠50mg	AST、ALT,gGTP、T-Bil　の全4項目
甲状腺機能障害	ヴォトリエント錠200mg スチバーガ錠40mg インライタ錠1mg インライタ錠5mg スーテントカプセル12．5mg	TSH、fT3、fT4 のいずれか
眼障害	アミオダロン塩酸塩速崩錠100mg アミオダロン塩酸塩速崩錠50mg	細隙灯検査

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定期検査推奨アラート

- アラート対象処方を受けた患者数：
  - 導入前　415人(1.1%)
  - 導入後　309人 (1.5%)
- アラートを受けた患者数：
  - 導入前　223人 (54%)
  - 導入後　149人 (48%)

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アラート別患者数

- 眼検査推奨アラートを受けた患者数:
  導入前　64人 (29%)
  導入後　45人 (30%)
- 甲状腺機能検査推奨アラートを受けた患者数:
  導入前　11人 (4.9%)
  導入後　2人 (1.3%)
- 肝機能検査推奨アラートを受けた患者数:
  導入前　155人 (70%)
  導入後　104人 (70%)

HYOGO COLLEGE OF MEDICINE

アラート稼働薬剤

薬剤名	導入前			導入後		
	処方数 (n=2,266)	アラート数 (n=1,831)	検査数 (n=99)	処方数 (n=590)	アラート数 (n=239)	検査数 (n=20)
エクア錠50mg	1701	643 (38)	77 (12)	452	149 (33)	15 (10)
アミオダロン塩酸塩速崩錠 (100mg)	311	271 (87)	7 (2.6)	79	65 (82)	2 (3)
アミオダロン塩酸塩速崩錠 (50mg)	140	118 (84)	3 (2.5)	32	22 (69)	1 (4.5)
スチバーガ錠40mg	64	38 (59)	11 (29)	12	3 (25)	2 (67)
スーテントカプセル12．5mg	39	6 (15)	0 (0)	12	0 (0)	0 (0)
ヴォトリエント錠200mg	7	5 (71)	1 (20)	11	0 (0)	0 (0)
インライタ錠1mg	0	0 (0)	0 (0)	2	0 (0)	0 (0)
インライタ錠5mg	4	0 (0)	0 (0)	1	0 (0)	0 (0)

HYOGO COLLEGE OF MEDICINE

薬物療法支援ガイドー骨粗鬆症

HYOGO COLLEGE OF MEDICINE

ガイドラインに基づく臨床支援決断システムⅠ
＜原発性骨粗鬆症＞

対象：原発性骨粗鬆症又は骨粗鬆症の病名を有する患者
骨粗鬆症診療ガイドライン2015に基づき以下の予防医療喚起を行う

A. 過去１年以内に骨密度検査がない場合
→　骨密度検査を推奨

B. ビスホスホネート初回投与時*
→過去3か月以内に血清Ca, P, Mg, Cre, BUN及び骨密度検査が無い場合には同検査を推奨

過去三か月に同処方のない者

HYOGO COLLEGE OF MEDICINE

骨粗鬆症患者

- 骨粗鬆症患者:
  導入前　411人 (1.1%)
  導入後　325人 (1.6%)

- 骨密度検査推奨アラートを受けた患者数:
  導入前　313人 (76%)
  導入後　216人 (66%)

HYOGO COLLEGE OF MEDICINE

骨密度検査推奨アラート

- ビスホスホネート総処方数:
  導入前　2,182件
  導入後　629件
- 骨粗鬆症の診断名下のビスホスホネート処方数:
  導入前　2,077件 (95%)
  導入後　573件 (91%)
- 骨密度検査推奨アラート稼働回数:
  導入前　1,586件 (73%)
  導入後　353件 (56%)
- 検査実施回数:
  導入前　68件 (4.3%)
  導入後　38件 (11%)

HYOGO COLLEGE OF MEDICINE

ガイドラインに基づく臨床支援決断システムI
＜原発性骨粗鬆症＞

対象：原発性骨粗鬆症又は骨粗鬆症の病名を有する患者
骨粗鬆症診療ガイドライン2015に基づき以下の予防医療喚起を行う

A. 過去1年以内に骨密度検査がない場合
→　骨密度検査を推奨

B. ビスホスホネート初回投与時*
→過去3か月以内に血清Ca, P, Mg, Cre, BUN及び骨密度検査が無い場合には同検査を推奨
**過去三か月に同処方のない者*

HYOGO COLLEGE OF MEDICINE

ビスホスホネート初回投与

- ビスホスホネート初回投与患者：
  導入前　131人 (0.4%)
  導入後　59人 (0.3%)

- 検査推奨アラートを受けた患者数：
  導入前　127人 (97%)
  導入後　54人 (92%)

HYOGO COLLEGE OF MEDICINE

ビスホスホネートアラート

- ビスホスホネート総処方数:
  導入前　2,182件
  導入後　629件
- ビスホスホネート初回投与件数:
  導入前　136件 (6%)
  導入後　60件 (10%)
- 初回投与に対する検査推奨アラート稼働回数:
  導入前　131件 (96%)
  導入後　54件 (90%)
- 検査実施回数:
  導入前　0件 (0%)
  導入後　9件 (17%)

HYOGO COLLEGE OF MEDICINE

ガイドラインに基づく臨床支援決断システムⅡ ＜ステロイド性骨粗鬆症＞

対象:経口ステロイドを3か月以上使用中の外来患者

骨粗鬆症診療ガイドライン2015に基づき以下の予防医療喚起を行う

A. ステロイド性骨粗鬆症の薬物療法開始基準1-6に該当する場合

→ビスホスホネート処方を推奨

B. ステロイド性骨粗鬆症の薬物療法開始基準に該当しない場合

→骨折歴を確認を推奨

C. 過去一年間骨密度測定が実施されていない場合

→骨密度測定を推奨

危険因子		スコア
既存骨折	なし	0
	あり	7
年齢(歳)	<50	0
	50≦ <65	2
	≧65	4
ステロイド投与量(PSL換算mg/日)	<5	0
	5≦ <7.5	1
	≧7.5	4
腰椎骨密度(%YAM)	≧80	0
	70≦ <80	2
	<70	4

*ステロイド性骨粗鬆症の薬物療法開始基準**

1. ステロイド投与量(PSL換算)7.5mg/日以上
2. 65歳以上
3. 50歳以上＆ステロイド投与量(PSL換算)5mg/日以上
4. 骨密度†70%以下
5. 骨密度† 70～80%＆ステロイド投与量5.0mg/日以上
6. 骨密度† 70～80%＆50歳以上

*対象:経口ステロイド3か月以上使用中の患者
† 一年以内かつ直近の骨密度

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ステロイド使用(3か月≤)患者

- ステロイド使用患者(3か月以上):
  導入前　535 (1.4%)
  導入後　432人 (2.1%)
- ビスホスホネート投与推奨アラートを受けた患者数:
  導入前　306人 (57%)
  導入後　214人 (50%)
- 骨折歴確認推奨アラートを受けた患者数:
  導入前　139人 (26%)
  導入後　91人 (21%)
- 骨密度検査推奨アラートを受けた患者数:
  導入前　495人 (93%)
  導入後　374人 (87%)

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ステロイド処方数

- ステロイド総処方数:
  導入前　5,461件
  導入後　1,469件
- 3か月以上使用中のステロイド処方数:
  導入前　3,752件 (69%)
  導入後　1,039件 (71%)

	導入前		導入後	
	アラート数	処方(検査)数	アラート数	処方(検査)数
ビスホスホネート投与推奨	1,763	82 (4.7)	478	33 (7)
骨密度測定推奨	3,339	132 (4.0)	766	91 (12)

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結　語

- 決断支援システム導入前の1年間について、研究計画通りに順調にバックグランドデータが蓄積された
- 臨床決断支援システム導入後、3か月間の経過では、臨床現場に大きなトラブルもなく、計画通りにシステムが稼働していることが確認できた
- 支援システム導入後3か月間の中間解析において、支援に応じた処方変更や追加検査の増加傾向が認められており、システム導入が患者のヘルスアウトカムに大きな効果を及ぼすことが期待された

総合討論

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Association between heart rate on admission and in-hospital mortality among general inpatients

Insights from Japan Adverse Drug Events (JADE) study

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Abstract

Association between heart rate (HR) and in-hospital mortality in general patients irrespective of underlying diseases were not well scrutinized. We assessed the relationship between HR on admission and in-hospital mortality among general inpatients.

We used data from Japan Adverse Drug Events (JADE) study, a prospective cohort study. One tertiary care hospital in Japan with 13 medical and 12 surgical wards, and an intensive care unit (ICU). Patients (n = 2360) were ≥12 years old and admitted to this hospital within 3 months; and pregnant women were excluded. We assessed the relationship between HR and mortality in five (<60, 60–79, 80–99, 100–119, ≥120 beats per minutes [bpm]) groups. We also compared the five HR groups according to the age (<70 years; ≥70 years) and wards (medical; surgical; ICU).

We enrolled 2360 patients (median age, 71 [interquartile range (IQR) 58–81] years) including 1147, 1068, and 145 patients in the medical and surgical wards, and the ICU, respectively. The median (IQR) HR on admission was 78 (68–91) bpm. Ninety-five patients died during hospitalization. Mortalities in the <60, 60–79, 80–99, 100–119, and ≥120 bpm groups were 2.9% (5/175), 2.7% (28/1047), 3.4% (26/762), 8.2% (24/291), and 14.3% (12/84), respectively ($P < .001$). The adjusted odds ratios of in-hospital mortality was 3.64 (95% CI 1.88–7.05, $P < .001$) when HR was ≥100 bpm in the medical ward; and 5.69 (95% CI 1.72–18.82, $P = .004$) when HR ≥120 bpm in the surgical ward. There was no statistically significant relationship with the ICU.

In conclusion, higher HR should be associated with in-hospital mortality among patients with general diseases. Even with less severe condition or outside ICU, HR should be directed attention to and patients with high HR on admission should be taken additional therapy to reduce the further risk of deterioration.

Abbreviations: bpm = beats per minutes, HR = heart rate, ICU = intensive care unit, IQR = interquartile range, JADE study = Japan Adverse Drug Events study, OR = odds ratio.

Keywords: heart rate, Japan Adverse Drug Events (JADE) study, mortality

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The authors have no conflicts of interest to disclose.

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1. Introduction

High heart rate (HR) is associated with cardiovascular mortality and all-cause mortality in the general population.[1–3] A recent meta-analysis reported the relative risk of having 10 beats per minutes (bpm) resting HR as 1.08 (95% CI 1.06–1.10) for cardiovascular mortality among the general population.[1] The association between HR and in-hospital mortality has also been reported in patients with cardiovascular comorbidities.[4] Patients with acute ischemic stroke and HR ≥83 bpm on admission had higher risk of in-hospital mortality with adjusted odds ratio (OR) of 4.42.[4] However, the association between HR and in-hospital mortality in general patients irrespective of underlying diseases were not well scrutinized.

With any relationship between HR and in-hospital mortality, or any threshold to trigger it, the risk in such patients could be addressed to reduce mortality efficiently. In addition, any intervention aimed at reducing HR, or the sympathetic nervous system, might offer supplementary therapy for patients with abnormal HR on admission. Thus, we analyzed data from a prospective cohort study to clarify the association between HR and in-hospital mortality among general patients.

2. Methods

2.1. Study design and patient population

The Japan Adverse Drug Events (JADE) study involves series of cohort studies conducted to evaluate adverse drug events and medication errors in Japan.[5–8] In this study, we used the data from a tertiary care hospital. There were 13 medical and12 surgical wards, and an intensive care unit (ICU). We included patients aged ≥12 years old, admitted to this hospital during a 3-month period from September through November 2013, while excluding pregnant women; because they were generally considered healthy people. Those aged <12 years were excluded because the median HR among them was higher than those ≥12 years.[9] Patients were followed-up until transfer, discharge, or death. The study protocol complied with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects issued by the Ministry of Health, Labor, and Welfare in Japan.

The institutional review board of the hospital approved the study and the board waived the requirement of informed consent because all data were obtained as part of daily routine practice.

2.2. Data collection and definitions

In the JADE study, data on all clinical symptoms and signs as well as laboratory data were extracted from the electronic medical record from the admission to the discharge. Because patients were admitted due to a number of diseases or medical conditions, we categorized the primary diseases on admission into 15 groups by the International Classification Diseases 10th revision.[10]

The study primary endpoint was in-hospital mortality, and HR at admission was compared with in-hospital mortality. HR was treated as a continuous variable or categorized into five (<60, 60–79, 80–99, 100–119, ≥120 bpm) groups; because we hypothesized that there was threshold to the risk of mortality. We analyzed the relationship between HR and mortality as a whole, stratified by the age (<70 years; ≥70 years) and wards (medical; surgical; ICU). The threshold of age was determined by the median value. The missing values were treated as missing without imputations and we analyzed the data without the missing variables.

2.3. Statistical analyses

The descriptive statistics were shown as median (interquartile range [IQR]) for continuous variables, and as numbers and percentages for categorical variables. We used Wilcoxon rank sum test or chi-square test to compare patients' characteristics between "died" and "survived" patients. We compared HR groups and mortalities by chi-square test.

To assess the association between HR on admission and in-hospital mortality adjusted for possible confounders, we constructed multivariable logistic regression models including the following independent variables; age, gender, systolic blood pressure, hemoglobin, total protein, creatinine, and white blood cell count as well as HR. Because there were a number of diseases or medical conditions, we could not adjust for such comorbidities, rather, we stratified by wards and adjusted the surrogates, which were associated with the severity in patients. We constructed four models by treating HR as continuous or dichotomized variable with different thresholds. We conducted all analyses using JMP 13.1 (SAS Institute Inc., Cary, NC, USA) software. Two tailed P-values $< .05$ were considered statistically significant.

3. Results

We enrolled 2360 patients among the 3120 patients who were admitted during the study period. We excluded 365 patients with pregnancy or pregnancy complications, and another 395 patients who were <12 years old. The median age was 71 (IQR, 58–81) years; and men accounted for 54% (1266) (Table 1). The median HR was 78 (IQR 68–91) bpm. The missing values occurred in two patients with HR, and were generally observed in <100 patients for other variables, aside respiratory rate (1031), total bilirubin (108), γ-glutamyltranspeptidase (760), lactate dehydrogenase (272), alkaline phosphatase (538), and creatinine kinase (854). Common diseases or medical conditions included the circulatory system (26.7%), neoplasms (21.8%), and digestive system (19.4%) in the medical wards; neoplasms (33.2%), injury, poisoning, and certain other consequences of external causes (19.9%); and digestive system (13.2%), in the surgical wards; and injury, poisoning, and certain other consequences of external causes (38.6%), respiratory system (15.2%), and circulatory system (12.4%), in the ICU (Table 2).

During the hospital stay, the 95 patients who died were older than those who survived (median: 83 vs 70 years, $P < .001$). Median HR among dead patients was higher than those who survived (92 vs 78 bpm, $P < .001$) (Table 1). Patients who died during the hospital stay had significantly lower blood pressure, lower hemoglobin level, higher white blood cell count, higher urea nitrogen level, and higher lactate dehydrogenase level (Table 1).

Overall, in-hospital mortality was significantly elevated when the HR increased (Fig. 1A). Among patients with age less than 70 years, mortality in the ≥120 groups was 12.1% (4/33) ($P < .001$; Fig. 1B), whereas those ≥70 years, mortality in the 100–119 and ≥120 groups were 12.2% (20/164) and 15.7% (8/51) ($P < .001$; Fig. 1C), respectively.

In terms of wards, significant associations were observed in the medical and surgical wards (Fig. 2A and B, respectively). Mortalities in the <60, 60–79, 80–99, 100–119, and ≥120 groups were 0% (0/90), 2.3% (11/484), 3% (11/367), 10.7% (18/169), and 10.8% (4/37) in the medical wards, respectively ($P < .001$; Fig. 2A). In the surgical wards, for the ≥120 group, this was 14.8% (4/27) ($P = .009$; Fig. 2B). Although mortalities in the <60 and ≥120 groups were relatively high in the ICU (30% [3/10] and 20% [4/20]), the difference was not statistically significant ($P = .31$; Fig. 2C).

Multivariable logistic regression model showed that the adjusted OR for one increment in HR was 1.03 (95% CI 1.01–1.04, $P < .001$) in the medical ward and 1.02 (95% CI 1.00–1.04, $P = .03$) in the surgical ward, but not statistically significant in the ICU (Table 3, Model 1). With HR ≥100 bpm, adjusted OR for this category compared to HR <100 bpm was 3.64 (95% CI 1.88–7.05, $P < .001$) in the medical ward; however, this was not statistically significant in the surgical wards ($P = .10$) and ICU ($P = .30$) (Table 3, Model 2). Similarly, at HR ≥120, adjusted OR was 5.69 (95% CI 1.72–18.82, $P = .004$) compared to HR <120 bpm in surgical ward, but not statistically significant in medical ward ($P = .10$) or ICU ($P = .70$) (Table 3, Model 3). There was no association between HR <60 bpm and in-hospital mortality either in the medical ($P = .81$) or surgical wards ($P = .80$), or ICU ($P = .30$) (Table 3, Model 4).

Table 1

Patient characteristics.

Variables	All patients (n = 2360)	Died (n = 95)	Survived (n = 2265)	*P*-value
Age (years), median (IQR)	71 (58–81)	83 (74–89)	70 (57–80)	<.001
Male, n (%)	1266 (54)	53 (56)	1213 (54)	.70
Heart rate (beats per minute), median (IQR)	78 (68–91)	92 (77–109)	78 (68–90)	<.001
Systolic blood pressure (mm Hg), median (IQR)	127 (112–145)	121 (99–146)	127 (112–145)	.03
Diastolic blood pressure (mm Hg), median (IQR)	74 (65–85)	70 (59–83)	74 (65–85)	.007
Respiratory rate (/min), median (IQR)	19 (16–23)	22 (18–26)	19 (16–23)	<.001
Hemoglobin (g/dL), median (IQR)	12.7 (11.0–14.1)	11.2 (8.7–13.1)	12.7 (11.1–14.1)	<.001
Hematocrit (%), median (IQR)	37 (32.6–40.7)	32.9 (25.9–38.5)	37.1 (32.9–40.7)	<.001
White blood cell (/μL), median (IQR)	6510 (5000–9098)	9040 (6310–13050)	6440 (4970–8945)	<.001
Platelet ($\times 10^4$/μL), median (IQR)	19.5 (15.6–24.2)	16.8 (11.7–22.5)	19.6 (15.8–24.3)	.002
Serum glucose concentration (mg/dL), median (IQR)	112 (97–139)	127 (101–193)	112 (97–138)	.006
Na (mmol/L), median (IQR)	139.2 (136.9–140.8)	136.7 (133.8–140.5)	139.2 (137.1–140.8)	.001
K (mmol/L), median (IQR)	4.1 (3.8–4.4)	4.2 (3.5–4.7)	4.1 (3.8–4.4)	.50
Cl (mmol/L), median (IQR)	103.0 (100.5–104.9)	100.0 (96.5–104.1)	103.0 (100.7–104.9)	<.001
Urea nitrogen (mg/dL), median (IQR)	15.2 (11.9–20.8)	28.1 (19.1–45.4)	15.0 (11.8–20.2)	<.001
Creatinine (mg/dL), median (IQR)	0.78 (0.63–0.98)	1.02 (0.75–1.62)	0.77 (0.63–0.96)	<.001
Total protein (g/dL), median (IQR)	6.8 (6.4–7.2)	6.3 (5.6–6.8)	6.8 (6.4–7.2)	<.001
Total bilirubin (mg/dL), median (IQR)	0.7 (0.5–1.0)	0.7 (0.5–1.2)	0.7 (0.5–1.0)	.06
Aspartate aminotransferase (U/L), median (IQR)	22 (17–31)	36 (24–91)	22 (17–30)	<.001
Alanine aminotransferase (U/L), median (IQR)	17 (12–26)	23 (14–47)	16 (12–25)	<.001
γ-Glutamyltranspeptidase (U/L), median (IQR)	26 (16–52)	34 (18–113)	26 (16–50)	.03
Lactate dehydrogenase (U/L), median (IQR)	212 (179–264)	317 (257–465)	209 (178–257)	<.001
Alkaline phosphatase (U/L), median (IQR)	243 (190–313)	320 (222–516)	242 (189–310)	<.001
Creatine kinase (U/L), median (IQR)	77 (50–131)	86 (36–200)	77 (50–130)	.50
Estimated glomerular filtration rate (mL/min/1.73 m^2), median (IQR)	68.6 (53.1–83.5)	46.5 (31.0–66.3)	69.4 (54.0–84.0)	<.001

IQR = interquartile range.

4. Discussion

Similar to previous reports in the general population or among patients with specific diseases, we found higher HR was associated with higher in-hospital mortality among general in patients. This association was statistically significant in the medical and surgical wards with adjusted ORs of one bpm increment of 1.03 and 1.02, respectively. The threshold in this cohort was 100 bpm in the medical and 120 bpm in the surgical wards. However, such thresholds, either higher or lower ones, were not apparent in the ICU, although some lower and higher threshold values were graphically implied.

Recent meta-analysis showed that the general people with resting HR of ≥80 bpm had higher risk of cardiovascular and all-cause mortality with relative risks of 1.33 and 1.45, respectively.[2] Another meta-analysis showed that the resting HR was an independent predictor of coronary artery disease (hazard ratio:

Table 2

Conditions on admission.

Conditions on admissions	All patients, n (%) (n = 2360)	Medical wards, n (%) (n = 1147)	Surgical wards, n (%) (n = 1068)	Intensive care unit, n (%) (n = 145)
Certain infectious diseases	76 (3.2)	55 (4.8)	4 (0.4)	17 (11.7)
Neoplasms	605 (25.6)	250 (21.8)	355 (33.2)	0 (0)
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	19 (0.8)	13 (1.1)	5 (0.5)	1 (0.7)
Endocrine, nutritional and metabolic diseases	62 (2.6)	43 (3.7)	7 (0.7)	12 (8.3)
Mental and behavioral disorders	51 (2.2)	42 (3.7)	2 (0.2)	7 (4.8)
Diseases of the nervous system	48 (2.0)	26 (2.3)	13 (1.2)	9 (6.2)
Diseases of the eye and adnexa	45 (1.9)	1 (0.1)	44 (4.1)	0 (0)
Diseases of the ear and mastoid process	19 (0.8)	1 (0.1)	18 (1.7)	0 (0)
Diseases of the digestive system	364 (15.4)	222 (19.4)	141 (13.2)	1 (0.7)
Diseases of the circulatory system	417 (17.7)	306 (26.7)	93 (8.7)	18 (12.4)
Diseases of the respiratory system	194 (8.2)	112 (9.8)	60 (5.6)	22 (15.2)
Diseases of the genitourinary system	109 (4.6)	35 (3.1)	73 (6.8)	1 (0.7)
Diseases of the skin and subcutaneous tissue	32 (1.4)	13 (1.1)	19 (1.8)	0 (0)
Diseases of the musculoskeletal system and connective tissue	28 (1.2)	6 (0.5)	21 (2.0)	1 (0.7)
Injury, poisoning, and certain other consequences of external causes	291 (12.3)	22 (1.9)	213 (19.9)	56 (38.6)

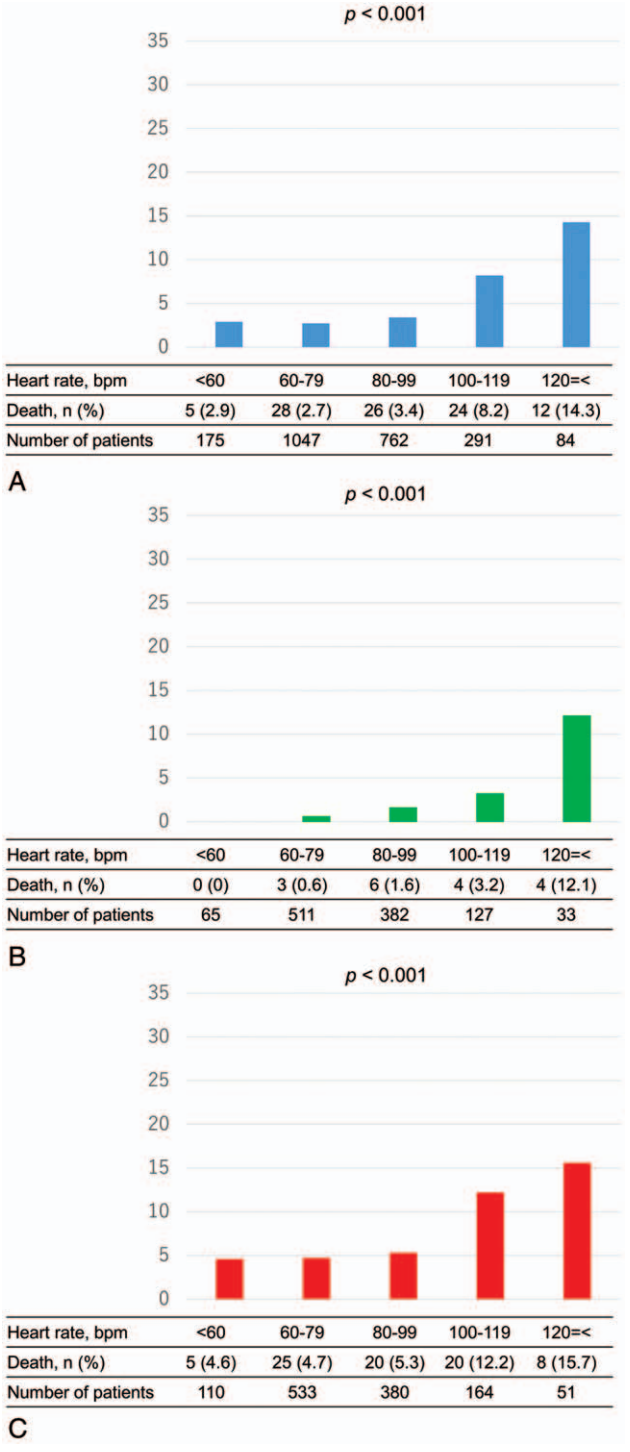

Figure 1. Heart rate on admission and in-hospital mortality in total cohort and according to age. (A) All patients; (B) patients younger than 70 years old; (C) patients equal to or older than 70 years old.

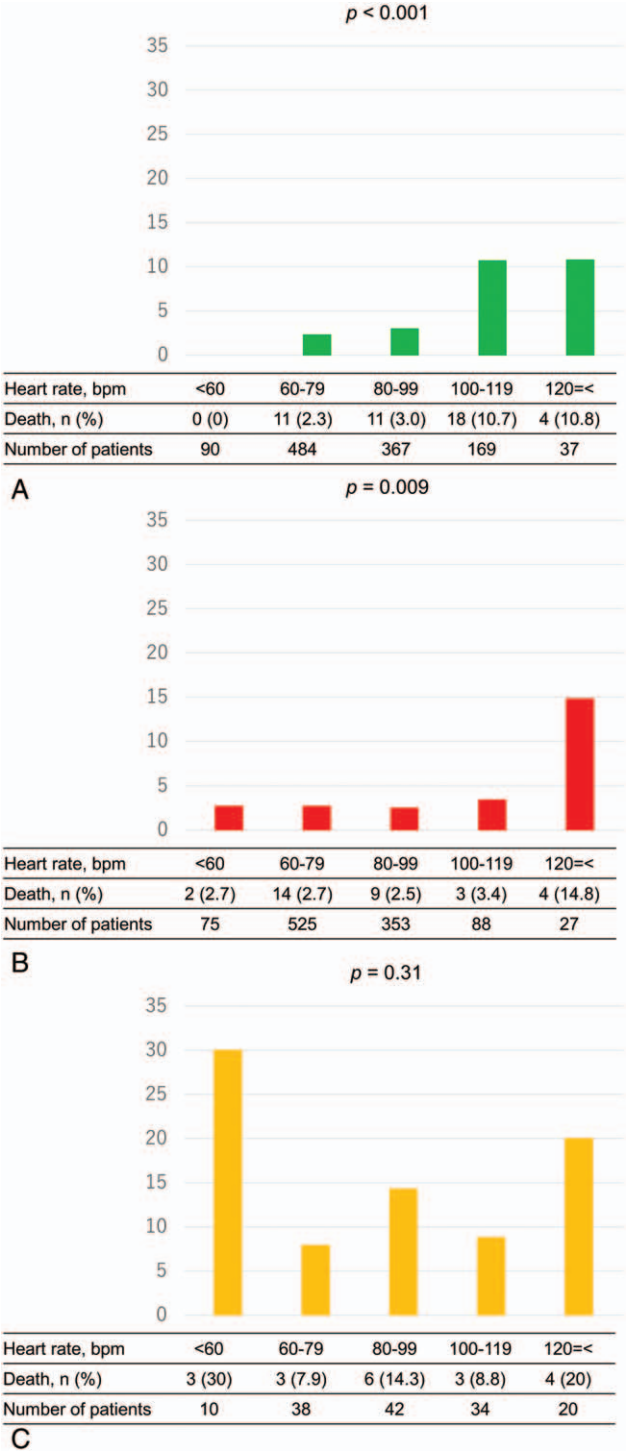

Figure 2. Heart rate on admission and in-hospital mortality according to ward. (A) Medical wards; (B) surgical wards; (C) intensive care unit.

1.12), stroke (HR, 1.05), all cancer types (hazard ratio, 1.09), and other diseases (hazard ratio, 1.25).[2] Long-term follow-up cohort from the Framingham Heart Study also reported the association between higher HR and cardiovascular events with hazard ratio of 1.15 for 11 bpm increment in the baseline HR during a median follow-up of 19 years.[11] The hazard ratio (1.32) for the same increment in HR was also reported for heart failure.[11] These observations were derived from epidemiological studies among the general population, but other reports also suggested the associations among inpatients similar to our reports.

The association between baseline HR and in-hospital mortality has been reported in patients with cardiovascular diseases. HR on

Table 3

Multivariable model for the effect of heart rate on in-hospital mortality.

	Medical ward (n = 1147)			Surgical ward (n = 1068)			Intensive care unit (n = 145)		
	Adjusted odds ratio	95% confidence interval	*P*-value	Adjusted odds ratio	95% confidence interval	*P*-value	Adjusted odds ratio	95% confidence interval	*P*-value
Model 1									
Heart rate (bpm)	1.03	1.01–1.04	< .001	1.02	1.00–1.04	.03	0.99	0.97–1.02	.50
Age (years)	1.06	1.03–1.10	< .001	1.04	1.01–1.08	.009	1.12	1.04–1.22	.01
Men	1.08	0.55–2.10	.80	2.44	1.09–5.48	.03	4.21	1.02–17.42	.05
Systolic blood pressure (mm Hg)	0.98	0.97–0.997	.02	1.01	0.995–1.02	.20	0.997	0.98–1.02	.70
Hemoglobin (g/dL)	0.90	0.78–1.04	.10	0.82	0.68–0.99	.04	0.74	0.51–1.04	.09
Total protein (g/dL)	0.66	0.45–0.97	.04	0.84	0.47–1.53	.60	0.30	0.11–0.69	.01
Creatinine (mg/dL)	1.12	0.92–1.30	.20	1.17	0.75–1.60	.40	1.05	0.60–1.70	.90
White blood cell (/μL)	1.00	0.999–1.00	.30	1.00	0.999–1.00	.20	1.00	0.999–1.00	.30
Model 2									
Heart rate ≥100 bpm	3.64	1.88–7.05	< .001	2.04	0.78–5.31	.10	0.52	0.14–1.95	.30
Age (year)	1.06	1.03–1.10	< .001	1.04	1.01–1.08	.01	1.13	1.05–1.24	.01
Men	1.10	0.56–2.15	.80	2.17	0.98–4.77	.06	4.38	1.04–18.43	.04
Systolic blood pressure (mm Hg)	0.98	0.97–0.997	.02	1.01	0.997–1.03	.10	0.997	0.98–1.02	.80
Hemoglobin (g/dL)	0.9	0.78–1.03	.10	0.84	0.69–1.01	.06	0.74	0.51–1.05	.10
Total protein (g/dL)	0.65	0.44–0.95	.03	0.68	0.39–1.20	.20	0.30	0.11–0.69	.01
Creatinine (mg/dL)	1.12	0.91–1.30	.20	1.18	0.76–1.60	.40	1.03	0.59–1.68	.90
White blood cell (/μL)	1.00	0.999–1.00	.30	1.00	0.999–1.00	.20	1.00	0.999–1.00	.30
Model 3									
Heart rate ≥120 bpm	2.56	0.80–8.19	.10	5.69	1.72–18.82	.004	1.37	0.28–6.66	.70
Age (year)	1.06	1.03–1.10	< .001	1.04	1.01–1.08	.01	1.11	1.04–1.21	.01
Men	1.02	0.53–1.99	.90	2.19	0.992–4.84	.05	3.80	0.92–15.7	.06
Systolic blood pressure (mm Hg)	0.98	0.97–0.995	.008	1.01	0.997–1.03	.10	0.998	0.98–1.02	.80
Hemoglobin (g/dL)	0.90	0.79–1.04	.20	0.83	0.69–1.00	.06	0.71	0.48–1.02	.08
Total protein (g/dL)	0.60	0.41–0.87	.009	0.71	0.40–1.26	.20	0.31	0.12–0.71	.01
Creatinine (mg/dL)	1.11	0.91–1.29	.20	1.17	0.74–1.59	.40	1.07	0.62–1.73	.80
White blood cell (/μL)	1.00	0.999–1.00	.20	1.00	0.999–1.00	.10	1.00	0.999–1.00	.30
Model 4									
Heart rate <60 bpm	–	–	–	0.81	0.18–3.66	.80	2.73	0.43–17.24	.30
Age (year)	1.07	1.03–1.10	< 0.001	1.04	1.01–1.08	.01	1.11	1.04–1.21	.01
Men	0.98	0.51–1.91	1.00	2.27	1.03–4.97	.04	3.76	0.92–15.41	.07
Systolic blood pressure (mm Hg)	0.98	0.97–0.99	.006	1.01	0.997–1.03	.10	0.998	0.98–1.02	.80
Hemoglobin (g/dL)	0.91	0.79–1.05	.20	0.84	0.70–1.02	.08	0.73	0.50–1.02	.07
Total protein (g/dL)	0.61	0.41–0.89	.01	0.66	0.37–1.18	.20	0.30	0.11–0.69	.01
Creatinine (mg/dL)	1.12	0.92–1.29	.20	1.17	0.75–1.59	.40	1.08	0.62–1.76	.80
White blood cell (/μL)	1.00	0.999–1.00	.20	1.00	0.999–1.00	.10	1.00	0.999–1.00	.30

admission was associated with in-hospital mortality with hazard ratio of 4.42 for 10 bpm increment in HR, in patients with acute ischemic stroke. The recalculated OR for 10 bpm increment in HR in the medical wards in our study was 1.33, and the effect was smaller than that reported in patients with acute ischemic stroke. The reason for this discrepancy is probably because our study enrolled all patients including relatively healthier ones and thus the effect of HR was diluted by such patients.[4] Not only HR on admission, but high HR 24–36 h after admission was also associated with in-hospital mortality in patients with heart failure.[12] Although we did not find any relationship between HR on admission and in-hospital mortality in patients in ICU, mortality was reported to decrease in such patients when HR was kept less than 100 bpm within the first admission day.[13] Thus, to the best of our knowledge, there has been no report to suggest the existence of a relationship between HR and in-hospital mortality among the general patients; and our study is the first to address this important clinical issue.

The association between HR and mortality was well documented, but the reasons for this association were not well clarified.[14] Several explanations were proposed such as low physical fitness, higher blood pressure, or reduced variability in HR, and diminished baroreceptor sensitivity in those with high HR.[1,2,14] The immune or endocrine systems are impaired by the dysregulation of the autonomic nervous system in patients with chronic diseases, and HR variability is the indicator for the autonomic nervous system.[15–18] However, these explanations could not fully account for the pathophysiology of higher mortality, especially, within the context of short-term effect, observed among inpatients.

Association between baseline HR and in-hospital mortality should shed light on the effective risk stratification of inpatient care, among patients with cardiovascular diseases and the general inpatients. Patients with such elevated HR and with no apparent reasons for the high HR should be closely investigated to determine the reasons, and be monitored to prevent the deterioration of underlying diseases. This strategy could be more effective in the general medical or surgical wards, due to the apparent trend of in-hospital mortality in our study. On the other hand, this approach might not be effective in ICU, because ICU patients are being closely monitored due to their serious conditions already. Another approach is the use of medications,

which weakens the sympathetic nervous tone and decreases the HR. Such medications could be used as supplementary treatment to avoid fatality, in addition to therapy, targeting the underlying diseases. The effectiveness of beta-blockers in non-cardiac surgery patients remains controversial,[19] however, supportive treatments in this direction, should be investigated.

Several limitations must be addressed in this study. First, there were a number of diseases with significantly varied severity, in this cohort; because we enrolled all admitted adult patients. Mortality was primarily associated with underlying diseases and their severity. Because it was unrealistic to adjust for all disease categories in the multivariate models, we adjusted for the surrogate markers of mortalities such as blood pressure or critical laboratory parameters. Second, the number of patients were relatively small, especially in the ICU; therefore, the relationship, other than the categories used, might not have been well scrutinized. In addition, there were no statistically significant associations with the ICU. Third, we utilized the HR on admission only. HR changes over time and the first measurement of HR on the admission day might not be a precise indicator. However, there were no distinct rules to determine which timing of HR measurement is best for use as an indicator; therefore, it was inevitable to use the first measurement to stratify the patients' risk. Finally, the JADE study only enrolled Japanese patients; and this analysis utilized the data from just one hospital. To generalize and validate our results, it is necessary to conduct similar study with enough sample size in several settings.

5. Conclusion

We confirmed that higher HR was associated with higher in-hospital mortality among patients with general diseases in the medical and surgical wards. Even with less severe condition or outside ICU, HR should be directed attention to and patients with high HR on admission should be taken additional therapy to reduce the further risk of deterioration. Our findings should be attested to by further studies in other settings, or studies using interventional designs.

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RESEARCH ARTICLE Open Access

Clinical characteristics of pyogenic spondylitis and psoas abscess at a tertiary care hospital: a retrospective cohort study

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Abstract

Background: Psoas abscess and pyogenic spondylitis are intractable diseases that require long-term treatment, but the clinical characteristics and causative organisms have not been fully investigated. Herein, we describe the clinical characteristics of these diseases and evaluate the factors associated with in-hospital mortality and the presence of gram-negative rods as causative microorganisms.

Methods: All patients diagnosed with pyogenic spondylitis or psoas abscesses at a tertiary hospital were included. We retrieved the clinical data (age, sex, outcome, length of hospital stay, disease, bacteria, medication, comorbidities, and treatment status), vital signs (blood pressure, heart rate, and body temperature), and laboratory test results (blood cell count, liver function, renal function, electrolytes, blood sugar, and C-reactive protein) of all patients. The outcomes were in-hospital deaths and positive cultures of gram-negative rods.

Results: We analyzed 126 patients consisting of 69 (55%) men with a population mean age of 72 years. Seventy-two patients had pyogenic spondylitis and 54 had psoas abscesses. Eleven patients (8.3%) died during admission. The causative bacteria were gram-positive cocci in 63 patients (50%) and gram-negative bacteria in 19 patients (15%). The multivariate logistic model showed that blood urea nitrogen (BUN) (odds ratio [OR] 1.04, 95% confidence interval [CI] 1.02–1.06) and cardiovascular diseases (OR 7.02, 95% CI 1.55–31.8) were associated with in-hospital mortality. Platelets less than 150,000/μL (OR 3.14, 95% CI 1.02–9.65) and higher aspartic aminotransferase (OR 1.02, 95% CI 1.00–1.03) were associated with gram-negative rods.

Conclusions: Patients with suspected psoas abscesses or pyogenic spondylitis having a high BUN level and a history of cardiovascular diseases have a higher risk of mortality.

Keywords: Pyogenic spondylitis, Psoas abscess, Mortality

Background

Pyogenic spondylitis and psoas abscesses are caused by *Staphylococcus aureus*, often in areas with a low prevalence of tuberculosis [1–3]. Patients often have underlying diseases such as malignancies, diabetes mellitus, chronic renal failure, and cirrhosis, as well as long-term corticosteroid use [4–8]. These diseases are diagnosed using a combination of imaging techniques such as computed tomography (CT) or magnetic resonance imaging (MRI) and specimen cultures; however, diagnosis may often be difficult if the patient has few symptoms.

While some studies have reported the underlying diseases associated with pyogenic spondylitis and psoas abscesses [4–8], few have discussed the risk factors for a poor prognosis. It is also important to decide whether to administer antibiotics targeting gram-negative rods because bacteria other than *Staphylococcus* should be considered in some circumstances. Because clinical characteristics and risk factors associated with mortality or bacterial strains have not been well investigated, we described the clinical characteristics of patients with pyogenic spondylitis and psoas abscesses and investigated the factors associated with in-hospital deaths and the presence

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of gram-negative rods at the time of diagnosis. In addition, we compared the differences in clinical characteristics and outcomes between pyogenic spondylitis and psoas abscess, if any.

Methods

Study design and patients

We conducted a historical cohort study of all patients diagnosed with pyogenic spondylitis or psoas abscesses from 2000 to 2014 at Shimane Prefectural Central Hospital, a tertiary care hospital in Japan. Inclusion criteria were (1) patients who were diagnosed with pyogenic spondylitis or psoas abscesses by the physician in charge, (2) confirmation of the clinical diagnosis by radiological images, and (3) no apparent other causes that may mimic pyogenic spondylitis or psoas abscesses. There were no exclusion criteria. The diagnosis of pyogenic spondylitis and psoas abscess was confirmed using either CT or MRI. Bacteria associated with lesions or blood cultures were identified. Surgical interventions, such as percutaneous drainage, surgical drainage, and laminectomy, were determined by the physician in charge. The antimicrobial treatment was determined by the physician in charge based on the culture results and sensitivity analyses. Until the culture results were available or if the causative species could not be determined, empirical treatments based on established guidelines were administered.

We retrieved clinical data, vital signs, and laboratory test results of the patients from the Integrated Intelligent Management System database of Shimane Prefectural Central Hospital between August 1998 and August 2014. The Institutional Review Board of Shimane Prefectural Central Hospital approved this study. Since all data were obtained as part of our routine daily practice, informed consent was waived by the institutional review board.

Measurements

Clinical data included age, sex, the primary complaint, days from admission to diagnosis of pyogenic spondylitis or psoas abscess, and comorbidities (diabetes, hypertension, hyperlipidemia, cardiac disease, cerebrovascular disease, neurological disease, liver disease, renal disease, malignancy, and surgical history).

We also collected data regarding patient vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], heart rate, and body temperature) and laboratory test results (white blood cell count [WBC], hemoglobin, platelet cell count [Plt], C-reactive protein [CRP], aspartic aminotransferase [AST], alanine aminotransferase [ALT], blood sugar, serum albumin [Alb], total bilirubin, lactate dehydrogenase [LDH], blood urea nitrogen [BUN], creatinine [Cr], sodium, and potassium) at the time of diagnosis.

We also collected data regarding treatment modalities (intravenous antimicrobial use and surgical treatments), as well as in-hospital deaths and the length of time in the hospital.

Statistical analyses

Continuous variables are presented as the mean and standard deviation (SD) or median and interquartile range (IQR), and categorical variables as numbers and percentages. We compared continuous variables with the Student's t test or the Wilcoxon rank-sum test on the basis of the distributions. We compared categorical variables with the χ^2 test when appropriate; otherwise, we used Fisher's exact test. To explore the factors associated with in-hospital mortality and the presence of gram-negative rods, we constructed multivariate logistic regression models. We analyzed all patients to identify factors associated with in-hospital mortality but selected only culture-positive patients to investigate the factors associated with gram-negative rods.

Included continuous variables were unmodified; however, the units for WBCs and Plts were 100 and 10,000, respectively. For convenience, platelets were only analyzed if less than 150,000/μL. Potential variables were the measured clinical variables described above, and final models were determined after backward selection. Associations are expressed as odds ratio [OR] and 95% confidence intervals [CI]. All statistical analyses were performed using Stata12. All reported p values were two-tailed, and p values < 0.05 were considered statistically significant.

Results

Patient characteristics

A total of 126 patients (72 with pyogenic spondylitis [57%] and 54 with psoas abscesses [43%]) (Table 1) were studied. Their mean age was 72 ± 11 years (range 37–95 years). The number of male patients was 69 (55%). Lumbago or back pain was more frequent in pyogenic spondylitis (49 [68%] vs. 23 [43%], $p = 0.004$), whereas shock was more frequent in psoas abscesses (9 [17%] vs. 2 [2.8%], $p = 0.009$) (Table 1).

All 126 patients received antibiotic treatment. One patient received only oral antibiotics. A total of 54 (43%) patients received invasive interventions, and they were more frequent in psoas abscesses (29 [54%] vs. 25 [35%], $p = 0.045$). The invasive interventions included 50 percutaneous drainage (40%), 4 laminectomy (3.2%), and 2 surgical drainage (1.6%). Two patients received multiple treatments, one patient received percutaneous drainage and laminectomy, another patient received percutaneous drainage and surgical drainage.

There were 11 in-hospital deaths (8.7%). Although there was one death (0.8%) within 14 days and 10 deaths (7.9%) 14 days after admission, these were not statistically significant ($p = 0.82$). When we compared the

Table 1 Patients characteristics

	All *n* = 126	Pyogenic spondylitis *n* = 72	Psoas abscess *n* = 54	*p* value
Variables	*n* (%) or mean ± SD or median [IQR]			
Male	69 (55)	38 (53)	31 (57)	0.61
Age, year	72 ± 11	74 ± 10	70 ± 11	0.07
Length of stay, days	60 [39–97]	60 [41–106]	58 [36–94]	0.06
In-hospital death	11 (8.7)	3 (4.1)	8 (15)	0.05
Invasive interventions	54 (43)	25 (35)	29 (54)	0.045
Percutaneous drainage	50 (40)	21 (29)	29 (54)	0.006
Operation	6 (4.8)	5 (6.9)	1 (1.9)	0.24
Laminectomy	4 (3.2)	4 (5.6)	0 (0.0)	0.13
Surgical drainage	2 (1.6)	1 (1.4)	1 (1.9)	1.00
Days after admission to diagnosis, day	0 [0–11]	0 [0–5]	2 [0–20]	0.0167
Days after admission to diagnosis, day ≥ 14 days	28 (22)	10 (14)	18 (33)	0.016
Antibiotics use, days	28 [17–42]	28 [18–42]	30 [15–42]	0.79
Over 6 weeks	38 (30)	23 (32)	15 (28)	0.70
Symptoms				
Lumbago or back pain	72 (57)	49 (68)	23 (43)	0.004
Fever	51 (40)	32 (44)	19 (35)	0.30
Shock	11 (8.7)	2 (2.8)	9 (17)	0.009
Classification				
Type A*	–	33 (46)	–	–
Type B*	–	18 (25)	–	–
Type C*	–	21 (29)	–	–
Multiple abscesses	–	–	30 (56)	–
Co-morbidities	102 (81)	56 (78)	46 (85)	0.36
Hospitalized for comorbidity	57 (45)	27 (38)	30 (56)	0.044
Hospitalized for other infections	17 (13)	6 (8.3)	11 (20)	0.07
Bacterial detection	84 (67)	45 (63)	39 (72)	0.34
Gram-positive cocci	63 (50)	35 (49)	28 (52)	0.72
Gram-negative rods	19 (15)	8 (11)	11 (20)	0.15
Mycobacterium	2 (1.6)	2 (2.8)	0 (0.0)	0.51
Vital signs				
SBP, mmHg	132 ± 31	137 ± 28	127 ± 35	0.10
DBP, mmHg	75 ± 18	78 ± 15	70 ± 20	0.0151
Body temperature, °C	37.3 ± 1.1	37.4 ± 1.1	37.2 ± 1.1	0.27
Heart rate, /min	89 ± 19	88 ± 19	89 ± 19	0.30
Laboratory data				
WBC, $\times 10^2$/μL	113 ± 51	106 ± 41	122 ± 61	0.07
Hb, g/dL	11.3 ± 2.2	11.7 ± 1.8	10.7 ± 2.5	0.0116
Plt, $\times 10^4$/μL	22.8 ± 11.8	24.8 ± 11.5	20.0 ± 11.9	0.0234
CRP, mg/dL	11.1 ± 9.8	9.4 ± 8.4	13.3 ± 11.0	0.0233
T-bil, mg/dL	0.8 ± 0.5	0.8 ± 0.4	0.8 ± 0.5	0.75
Alb, g/dL	3.3 ± 0.6	3.4 ± 0.6	3.1 ± 0.7	0.0045
AST, IU/L	33 ± 30	31 ± 28	37 ± 31	0.26

Table 1 Patients characteristics *(Continued)*

	All *n* = 126	Pyogenic spondylitis *n* = 72	Psoas abscess *n* = 54	*p* value
ALT, IU/L	26 ± 23	26 ± 25	24 ± 19	0.73
LDH, IU/L	261 ± 123	239 ± 88	290 ± 153	0.0233
Blood sugar, mg/dL	152 ± 71	141 ± 66	165 ± 76	0.06
BUN, mg/dL	25.6 ± 22.8	20.9 ± 10.6	32.0 ± 32.0	0.0069
Cr, mg/dL	1.3 ± 1.7	1.0 ± 0.8	1.7 ± 2.5	0.0178
Na, mmol/L	137.0 ± 5.0	137.2 ± 5.1	136.7 ± 4.8	0.57
K, mmol/L	4.0 ± 0.6	4.0 ± 0.5	3.9 ± 0.7	0.42

*Classification by Pola et al. [17]

number of deaths before, and 60 days after admission, there were 6 deaths (4.8%) and 5 deaths (4.0%), respectively.

The number of patients who had comorbidities was 102 (81%), including 36 (29%) with hypertension, 32 (25%) with a surgical history, 21 (17%) with malignancies, 19 (15%) with diabetes, 15 (12%) with neurological diseases, 18 (14%) with cardiac disease, and 15 (12%) with cerebrovascular disease (Table 2).

Laboratory testing and physical examinations indicated that CRP (13.3 ± 11.0 vs. 9.4 ± 8.4 mg/dL, $p = 0.02$), LDH (290 ± 153 vs. 239 ± 88 IU/L, $p = 0.02$), BUN (32.0 ± 32.0 vs. 20.9 ± 10.6 mg/dL, $p = 0.007$), and Cr (1.7 ± 2.5 vs. 1.0 ± 0.8 mg/dL, $p = 0.02$) were higher in psoas abscess cases (Table 1).

Hospital courses

The median time from admission to diagnosis was 0 days (IQR 0–11, minimum 0 and maximum 185). In many cases, hospitalization occurred after the diagnosis of pyogenic spondylitis and psoas abscess (Table 1). The number of patients diagnosed with these diseases ≥ 14 days after hospitalization was 28 (22%) (median 31 days; IQR 21–50, minimum 14 and maximum 185). These patients developed pyogenic spondylitis or psoas abscesses during the course of hospitalization. There were 57 patients who were admitted for other comorbidities: medical department (40 patients) and surgical department (17 patients). Hospitalization for other infections were 17 patients. Comorbidities between pyogenic spondylitis and psoas abscess patients were generally similar (Table 2). Pyogenic spondylitis was diagnosed more rapidly than psoas abscesses (14% in ≥ 14 days vs. 33%, $p = 0.016$). The duration of antibiotics use was a median of 28 days (IQR 17–42, minimum 0 and maximum 206). Thirty-eight patients (30%) received intravenous antibiotics for 6 weeks. There was no statistical difference in the long-term use of antibiotics among patients ($p = 0.70$).

The median length of hospitalization was 60 days (IQR 39–97, minimum 4 and maximum 429). Eleven (8.7%) patients died during the hospitalization period.

Factors associated with in-hospital deaths included a lower SBP (110 ± 35 vs. 134 ± 30 mmHg, $p = 0.02$), a lower DBP (62 ± 19 vs. 76 ± 17 mmHg, $p = 0.03$), lower Alb (2.9 ± 0.8 vs. 3.3 ± 0.6 mg/dL, $p = 0.02$), higher AST (40 ± 19 vs. 33 ± 31 IU/L, $p = 0.02$), higher ALT (29 ± 11 vs. 25 ± 23 IU/L, $p = 0.04$), higher LDH (327 ± 114 vs. 254 ± 122 IU/L, $p = 0.01$), higher BUN (53.5 ± 45.3 vs. 22.9 ± 17.5 mg/dL, $p = 0.02$), and higher Cr (1.7 ± 0.9 vs. 1.3 ± 1.8 mg/dL, $p = 0.005$) (Table 3). The multivariate logistic model showed that BUN (OR 1.04, 95% CI 1.02–1.06) and cardiovascular disease (OR 7.02, 95% CI 1.55–31.8) were associated with in-hospital mortalities (Table 4).

Microbiological examinations

Causal microorganisms were identified in 85 patients (67%), including gram-positive bacteria in 63 patients (50%), gram-negative rods in 19 patients (15%), and others or undetermined (Table 5).

Factors associated with gram-negative rods included lower Plts (15.8 ± 9.6 vs. 22.9 ± 12.3 × 10,000/μL, $p = 0.0134$; Plt < 1.5×10^4/μL, 11 [58%] vs. 20 [30%], $p = 0.034$) and higher ASTs (57 ± 57 vs. 32 ± 23 IU/L, $p = 0.0236$) (Table 6). The multivariate logistic model showed that platelets less than 150,000/μL (OR 3.14, 95% CI 1.02–9.65) and higher aspartic aminotransferase (OR 1.02, 95% CI 1.00–1.03) were associated with gram-negative rods (Table 7).

Discussion

We showed the epidemiology of pyogenic spondylitis and psoas abscesses, as well as the factors associated with in-hospital mortality and the presence of gram-negative rods in patients' cultures at a single center. The factors associated with mortality were an elevated BUN and a history of cardiovascular disease. The factors associated with a positive culture of gram-negative rods included higher AST and lower Plt laboratory results.

Previous studies have reported that the predisposing factors for bacterial spondylitis or psoas abscesses were diabetes mellitus, malnutrition, substance abuse, human immunodeficiency virus infection, malignancy, long-term

Table 2 Co-morbidities of patients and status at hospitalization

	All	Pyogenic spondylitis	Psoas abscess	*p* value
	n = 126	*n* = 72	*n* = 54	
Variables	*n* (%)			
Co-morbidities	102 (81)	56 (78)	46 (85)	0.36
Diabetes	19 (15)	10 (14)	9 (17)	0.80
Hypertension	36 (29)	23 (31)	13 (24)	0.43
Hyperlipidemia	7 (5.6)	5 (6.9)	2 (3.7)	0.70
Cardiac diseases	18 (14)	8 (11)	10 (18)	0.31
Cerebrovascular disease	15 (12)	6 (8.3)	9 (17)	0.17
Neurological disease	15 (12)	8 (11)	7 (13)	0.79
Dementia	4 (3.2)	4 (5.6)	0 (0.0)	0.13
Alcoholism	4 (3.2)	1 (1.4)	3 (5.6)	0.31
Neurosis	2 (1.6)	1 (1.4)	1 (1.9)	1.00
Schizophrenia	2 (1.6)	0 (0.0)	2 (3.7)	0.18
Mental retardation	2 (1.6)	1 (1.4)	1 (1.9)	1.00
Depression	2 (1.6)	1 (1.4)	1 (1.9)	1.00
Epilepsy	1 (0.8)	0 (0.0)	1 (1.9)	0.43
Parkinson's disease	1 (0.8)	1 (1.4)	0 (0.0)	1.00
Pulmonary disease	7 (5.6)	3 (4.2)	4 (7.4)	0.46
Liver disease	7 (5.6)	4 (5.6)	3 (5.6)	1.00
Renal disease	8 (6.3)	3 (4.2)	5 (9.3)	0.29
Malignancy	21 (17)	9 (13)	12 (22)	0.16
Operation	32 (25)	17 (24)	15 (28)	0.68
Others	30 (24)	17 (24)	13 (24)	1.00
Osteoporosis	5 (4.0)	4 (5.6)	1 (1.9)	0.39
Pancreatitis	2 (1.6)	1 (1.4)	1 (1.9)	1.00
Thyroid disease	3 (2.4)	1 (1.4)	2 (3.7)	0.58
Inguinal hernia	1 (0.8)	0 (0.0)	1 (1.9)	0.43
Malignant syndrome	1 (0.8)	1 (1.4)	0 (0.0)	1.00
Hypoadrenalism	1 (0.8)	1 (1.4)	0 (0.0)	1.00
Gastrointestinal ulcer	4 (3.2)	2 (2.8)	2 (3.7)	1.00
Glaucoma	3 (2.4)	2 (2.8)	1 (1.9)	1.00
Discitis	1 (0.8)	1 (1.4)	0 (0.0)	1.00
Cholecystitis	1 (0.8)	1 (1.4)	0 (0.0)	1.00
Pemphigoid	1 (0.8)	1 (1.4)	0 (0.0)	1.00
Spinal stenosis	1 (0.8)	0 (0.0)	1 (1.9)	0.43
Rheumatoid arthritis	1 (0.8)	0 (0.0)	1 (1.9)	0.43
Reflux esophagitis	2 (1.6)	1 (1.4)	1 (1.9)	1.00
Ureteral stent placement	1 (0.8)	0 (0.0)	1 (1.9)	0.43
Common bile duct stone	1 (0.8)	1 (1.4)	0 (0.0)	1.00
Status at hospitalization				
Hospitalized for comorbidity	57 (45)	27 (38)	30 (56)	0.044
Medical department*	40 (32)	19 (26)	21 (39)	0.18
Surgical department**	17 (13)	8 (11)	9 (17)	0.43
Hospitalized for other infections	17 (13)	6 (8)	11 (20)	0.07
Urinary tract infection	7 (5.6)	1 (1.4)	6 (11)	0.042
Sepsis	4 (3.2)	2 (2.8)	2 (3.7)	1.00
Pneumonia	2 (1.6)	0 (0.0)	2 (3.7)	0.19
Cholangitis	1 (0.8)	1 (1.4)	0 (0.0)	1.00
Liver abscess	1 (0.8)	0 (0.0)	1 (1.9)	0.43
Pulmonary tuberculosis	1 (0.8)	1 (1.4)	0 (0.0)	1.00
Infectious arthritis	1 (0.8)	1 (1.4)	0 (0.0)	1.00

*Comorbidities treated at medical department: blood stream infection 1, cardio-pulmonary arrest 1, cerebral infarction 1, cholangitis 1, congestive heart failure 2, diabetes 1, drug eruption 1, fever of unknown origin 2, gastric ulcer 1, leukemia 1, liver abscess 1, lumbago 2, malignant lymphoma 1, myeloma 2, neuralgia 1, Paget disease 1, pneumonia 3, pulmonary tuberculosis 1, renal failure 3, schizophrenia 1, sepsis 3, skin damage 1, transient ischemic attack 1, urinary tract infection 7

**Comorbidities treated at the surgical department: abdominal trauma 1, burn injury 1, colon cancer 2, fall trauma 1, gastric cancer 2, hip pain 1, ileus 3, infectious arthritis 1, internal iliac artery aneurysm 1, knee pain 1, normal pressure hydrocephalus 1, subarachnoid hemorrhage 2

steroid use, chronic renal failure, liver cirrhosis, and sepsis [4–8]. Some reports have showed that CRP or WBCs were associated with recovery [9, 10], although our study showed that CRP was also associated with gram-negative rods.

Staphylococcus was found in 50–88% of patients in prior studies [3, 11, 12], and our study showed a similar percentage (60%). Among gram-negative bacteria identified in our study, *Escherichia coli* was found in 5.6%, which was slightly higher than the 2.8% reported in previous studies [11, 13]. *Mycobacterium tuberculosis* is a frequent cause of psoas abscesses in regions where tuberculosis is common (e.g., southern China) [1, 2]; however, the proportion of patients with tuberculosis among pyogenic spondylitis cases decreased to about 24% in these areas [3]. Tuberculosis is common in Japan, yet there was only one case of tuberculosis in our study, which may reflect an early diagnosis before progression to severe tuberculosis or before the incidence of tuberculosis decreased in Japan [14].

In previous studies, delay of treatment, old age, sepsis, and *E. coli* infection were reported as mortality risk factors [11, 15]. There were no differences in mortality between patients with and without gram-negative rods and between elderly and younger patients in our study. We assumed that all patients were promptly treated after the diagnosis. If the treatment was delayed, this factor might be associated with mortality. A previous report revealed an association between endocarditis and pyogenic spondylitis [16]; however, there were no cases of endocarditis

Table 3 Factors associated with in-hospital mortality

	Death ($n = 11$)	Alive ($n = 115$)	p value
Variables	n (%) or mean ± SD or median [IQR]		
Male	7 (64)	62 (54)	0.75
Age, year	73 ± 10	72 ± 11	0.80
Length of stay, days	57 [34–86]	60 [39–98]	0.68
Diseases			
Psoas abscess	8 (73)	46 (40)	0.038
Invasive interventions	6 (55)	48 (42)	0.31
Percutaneous drainage	6 (55)	44 (38)	0.23
Operation	1 (9.1)	5 (4.3)	0.43
Laminectomy	0 (0.0)	4 (3.5)	1.00
Surgical drainage	1 (9.1)	1 (0.9)	0.17
Co-morbidities	9 (82)	93 (81)	1.00
Diabetes	1 (9.1)	18 (16)	1.00
Hypertension	4 (36)	32 (28)	0.51
Hyperlipidemia	1 (9.1)	6 (5.2)	0.48
Cardiac diseases	4 (36)	14 (12)	0.05
Cerebrovascular disease	1 (9.1)	14 (12)	1.00
Neurological disease	2 (18)	13 (11)	0.62
Pulmonary diseases	0 (0.0)	7 (6.1)	1.00
Liver disease	0 (0.0)	7 (6.1)	1.00
Renal disease	1 (9.1)	7 (6.1)	0.53
Maligancy	2 (18)	19 (17)	1.00
Operation	1 (9.1)	31 (27)	0.29
Others	2 (18)	28 (24)	1.00
Bacteria			
Gram-positive cocci	7 (64)	56 (49)	0.53
Gram-negative rods	0 (0.0)	19 (17)	0.21
Unknown	3 (27)	38 (33)	1.00
Vital signs			
SBP, mmHg	110 ± 35	134 ± 30	0.0196
DBP, mmHg	62 ± 19	76 ± 17	0.0310
Body temperature, ℃	36.9 ± 1.1	37.4 ± 1.1	0.12
Heart rate, /min	93 ± 13	89 ± 19	0.33
Labo data			
WBC, $\times 10^2/\mu L$	115 ± 56	113 ± 51	0.88
Hb, g/dL	10.2 ± 2.8	11.4 ± 2.1	0.07
Plt, $\times 10^4/\mu L$	20.4 ± 18.8	23.0 ± 11.0	0.17
CRP, mg/dL	17.8 ± 12.2	10.4 ± 9.3	0.06
T-bil, mg/dL	1.1 ± 0.7	0.8 ± 0.5	0.11
Alb, g/dL	2.9 ± 0.8	3.3 ± 0.6	0.0220
AST, IU/L	40 ± 19	33 ± 31	0.0245
ALT, IU/L	29 ± 11	25 ± 23	0.0376
LDH, IU/L	327 ± 114	254 ± 122	0.0134
Blood sugar, mg/dL	156 ± 42	151 ± 73	0.26
BUN, mg/dL	53.5 ± 45.3	22.9 ± 17.5	0.0197
Cr, mg/dL	1.7 ± 0.9	1.3 ± 1.8	0.0053
Na, mmol/L	134.6 ± 10.0	137.3 ± 4.2	0.86
K, mmol/L	4.0 ± 0.5	4.0 ± 0.6	0.68

in our study. Psoas abscesses are generally reported to have higher morbidity and mortality. One study reported that the mortality rate of primary and secondary abscesses was 2.4% and 19%, respectively, and may approach 100% in untreated cases [1]. Our study had a similar mortality rate (15%), including primary and secondary psoas abscesses, although we could not differentiate them.

When the causative microorganism could not be identified, clinicians must administer an empirical treatment. The empirical treatment policy of the institution was following: (1) vancomycin ± cefazolin in general and (2) meropenem or similar antibiotics when gram-negative bacteria was likely in the setting of previous organism or infections of other sites. Those patients with an elevated BUN or cardiovascular comorbidity were at a higher risk of mortality. Therefore, such patients should receive broad-spectrum antibiotics as well as aggressive drainage and other intensive supportive therapies. The factors associated with gram-negative rods should also be a guide for empirical treatments. The prevalence of gram-negative rods was low, but those with lower platelet counts or elevated ASTs may be at a higher risk of gram-negative rod infections. These patients should receive antibiotics that target gram-negative rods as an initial therapy.

A new classification of pyogenic spondylodiscitis has been reported [17]. The new classification was based on clinical symptoms and radiological findings and associated with recurrence rate and mortality. Since our study had a retrospective design, we could not obtain the information necessary to reclassify our patients and our risk factors should be re-evaluated in future studies incorporating the new classification.

In this study, BUN and a history of cardiovascular disease were associated with in-hospital deaths. Low Plts

Table 4 Multivariate logistic model for death

	Odds ratio	95% confidence interval
BUN, mg/dL	1.04	1.02–1.06
Cardiovascular diseases	7.02	1.55–31.8

Table 5 Causative bacteria

Bacteria	All ($n = 126$)
	n (%)
Identified	85 (67)
Gram-positive cocci	63 (50)
Staphylococci	51 (40)
MSSA	28 (22)
MRSA	12 (9.5)
CNS	11 (8.7)
Enterococci	3 (2.4)
Streptococci	8 (6.3)
Gram-negative rods	19 (15)
Escherichia coli	7 (5.6)
Klebsiella	3 (2.4)
Prevotella	3 (2.4)
Proteus mirabilis	2 (1.6)
Citrobacter koseri	1 (0.8)
Bacteroides	4 (3.2)
Mycobacterium	2 (1.6)
Tuberculosis	1 (0.8)
Nontuberculosis	1 (0.8)
Other bacteria	2 (1.6)
Unknown	41 (33)

MSSA methicillin-sensitive *Staphylococcus aureus*, *MRSA* methicillin-resistant *Staphylococcus aureus*; *CNS* coagulase-negative *Staphylococcus*; *Enterocucci Enterococcus faecium* 1, *Enterococcus faecalis* 2; *Streptcocci* alpha-hemolytic *Streptococcus* 1, *Streptococcus agalactiae* (type B group) 3, *Streptococcus intermedius* 1, *Streptococcus sanguinis* 1, *Streptococcus pneumoniae* 2; *Klebsiella Klebsiella pneumoniae* 2, *Klebsiella oxytoca* 1; *Prevotella Prevotella oris* 1, *Prevotella melaninogenica* 1, unidentified 1; *Bacteroides Bacteroides fragilis* 3, *Bacteroides thetaiotaomicron* 1; other bacteria: Corynebacterium sp. 1

(< 150,000/μL) and high ASTs were associated with gram-negative rods after performing multivariate analyses. For the group with a higher risk of in-hospital mortality, aggressive drainage should be considered in addition to intensive antimicrobial combination therapy. Although the frequency of gram-negative rods was low, the use of wide-spectrum antibiotics should be considered for the group with a high probability of having gram-negative rods based on these risk factors.

This study has some limitations. First, since our study had a retrospective design, we were unable to measure all factors. Second, we investigated a total of 126 patients, and this sample size is insufficient for robust multivariate analyses. We also could not break down into small homogenous group due to small sample size. However, our primary purpose was to describe the general picture of patients who were diagnosed in daily practice. Third, since we focused solely on patients with pyogenic spondylitis or psoas abscesses and did not analyze all patients who presented with fever and lower

Table 6 Factors associated with gram-negative rods

	GNR ($n = 19$)	Others ($n = 66$)	*p* value
Variables	*n* (%) or mean ± SD or median [IQR]		
Male	13 (68)	33 (50)	0.20
Age, year	71 ± 9	72 ± 12	0.41
Psoas abscess	11 (58)	29 (44)	0.31
In hospital death	0 (0.0)	8 (12)	0.19
Invasive intervention	11 (58)	35 (53)	0.80
Percutaneous drainage	10 (53)	33 (50)	1.00
Operation	2 (11)	3 (4.5)	0.31
Laminectomy	2 (11)	2 (3.0)	0.22
Surgical drainage	0 (0.0)	1 (1.5)	1.00
Co-morbidities	15 (79)	52 (79)	1.00
Diabetes	3 (16)	9 (14)	0.73
Hypertension	5 (26)	12 (18)	0.52
Hyperlipidemia	2 (11)	3 (4.5)	0.31
Cardiac diseases	4 (21)	9 (14)	0.48
Cerebrovascular disease	5 (26)	8 (12)	0.15
Neurological disease	3 (16)	9 (14)	0.73
Pulmonary disease	0 (0.0)	4 (6.1)	0.57
Liver disease	1 (5.3)	4 (6.1)	1.00
Renal disease	0 (0.0)	4 (6.1)	0.57
Malignancy	1 (5.3)	12 (18)	0.28
Operation	6 (32)	17 (26)	0.77
Others	6 (32)	12 (18)	0.22
Vital signs			
SBP, mmHg	124 ± 27	131 ± 32	0.40
DBP, mmHg	75 ± 18	72 ± 16	0.58
Body tempereture, ℃	37.7 ± 1.3	37.4 ± 1.1	0.59
Heart rate, /min	91 ± 17	91 ± 20	0.83
Laboratory			
WBC, $\times 10^2/\mu L$	138 ± 69	120 ± 49	0.42
Hb, g/dL	11.8 ± 2.0	11.1 ± 2.1	0.16
Plt, $\times 10^4/\mu L$	15.8 ± 9.6	22.9 ± 12.3	0.0134
Plt < $1.5 \times 10^4/\mu L$	11 (58)	20 (30)	0.034
CRP, mg/dL	17.1 ± 9.5	12.6 ± 9.8	0.07
T-bil, mg/dL	1.0 ± 0.6	0.8 ± 0.4	0.18
Alb, g/dL	3.2 ± 0.6	3.2 ± 0.6	0.70
AST, IU/L	57 ± 57	32 ± 23	0.0236
ALT, IU/L	31 ± 23	27 ± 25	0.22
LDH, IU/L	292 ± 126	264 ± 108	0.37
Blood sugar, mg/dL	147 ± 83	157 ± 73	0.23
BUN, mg/dL	26.9 ± 14.9	25.2 ± 20.6	0.19
Cr, mg/dL	1.3 ± 1.2	1.3 ± 1.7	0.24
Na, mmol/L	136.9 ± 3.7	137.0 ± 4.7	0.86
K, mmol/L	4.0 ± 0.6	3.8 ± 0.5	0.66

GNR gram-negative rods

Table 7 Multivariate logistic model for gram-negative rods

	Odds ratio	95% confidence interval
Plt < 1.5×10^4/μL	3.14	1.02–9.65
AST, IU/L	1.02	1.00–1.03

back pain, there is a possibility of missed cases. However, considering that our institution is a teaching hospital with easy access to imaging technology, we believe that the number of missed cases is low. Fourth, bacteria were not identified in all cases. Therefore, factors related to gram-negative bacteria should be interpreted with caution. Fifth, there were no established protocols for antibiotics and surgical treatments because this study was a retrospective observational study. The effect of treatment modalities on mortality should be considered. Sixth, we could not classify the psoas abscesses as primary and secondary. If we had been able to differentiate between primary and secondary psoas abscesses, we might have indicated another risk factor for mortality as reported in the previous study. Seventh, there were many variables we compared between pyogenic spondylitis and psoas abscess. The issue of multiple comparisons and the resultant significance should be considered to interpret the results.

Conclusion

In clinical practice, pyogenic spondylitis and psoas abscesses are likely to be severe in the presence of low blood pressure, malnutrition, liver failure, and kidney dysfunction. When deciding which antibiotic to use, the possibility of gram-negative bacteria should be considered in patients with low Plts and liver dysfunction.

Abbreviations

Alb: Albumin; ALT: Alanine aminotransferase; AST: Aspartic aminotransferase; BUN: Blood urea nitrogen; CI: Confidence interval; CNS: Coagulase-negative Staphylococcus; Cr: Creatinine; CRP: C-reactive protein; CT: Computed tomography; DBP: Diastolic blood pressure; GNR: Gram-negative rods; IQR: Interquartile range; LDH: Lactate dehydrogenase; MRI: Magnetic resonance imaging; MRSA: Methicillin-resistant Staphylococcus aureus; MSSA: Methicillin-sensitive Staphylococcus aureus; OR: Odds ratio; Plt: Platelet cell count; SBP: Systolic blood pressure; SD: Standard deviation; WBC: White blood cell count

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Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author by request.

Authors' contributions

TN and TM designed the study and analyzed the datasets. TN, KoK, YY, JM, and KiK performed the data collection. TN and TM wrote and revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Review Board of Shimane Prefectural Central Hospital (R14–060). Since all data were obtained as part of our routine daily practice, informed consent was waived by the institutional review board.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interest.

Publisher's Note

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Effect of baseline renal and hepatic function on the incidence of adverse drug events: the Japan Adverse Drug Events study

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Abstract

Background: The impact of renal and hepatic dysfunction on the morbidity and mortality of inpatients with adverse drug events (ADEs) is uncertain in daily clinical practice. The objective of this study was to investigate the effect of renal and hepatic function on ADEs and inpatients' morbidity and mortality.

Methods: The Japan Adverse Drug Events (JADE) study was a prospective cohort study carried out at three tertiary-care teaching hospitals in Japan. Participants were consecutive inpatients (n = 3459) aged 15 years or older. We evaluated the effect of renal and hepatic function on the occurrence of ADEs, and assessed how they affected length of hospital stay (LOS) and in-hospital mortality. We used the estimated glomerular filtration rate to quantify renal function and categorized patients into three groups (normal, ≥60 mL/min/1.73 mm; moderate, ≥30 and <60 mL/min/1.73 mm; severe, <30 mL/min/1.73 mm). We defined patients as having hepatic dysfunction when at least one data point (total bilirubin, aspartate aminotransferase, alanine aminotransferase, or gamma glutamyltransferase) was beyond a cutoff value.

Results: We analyzed the laboratory data of 2508 patients. There was a significant difference in the occurrence of ADEs among the three GFR categories (normal, 20%; moderate, 26%; severe, 22%; p = 0.02). More ADEs occurred in patients with hepatic dysfunction (25% vs. 20%, p = 0.01). LOS was significantly longer in those with ADEs stratified either by renal or by hepatic dysfunction (p < 0.0001). ADEs were independently associated with in-hospital mortality, adjusting for renal and hepatic function (p < 0.0001).

Conclusions: Inpatients' organ dysfunction increased ADEs, and ADEs were associated with both LOS and in-hospital mortality independently, irrespective of renal and hepatic function.

Keywords: adverse drug events; hepatic function; JADE study; patient safety; renal function.

Introduction

Adverse drug events (ADEs) are injuries from medication usage [1, 2] and are a cause of morbidity, mortality, and hospitalization [1, 3]. Many inpatients with acute or chronic diseases need to take multiple medications for treatment. Because all medications pass through the processes of absorption, distribution, metabolism, and excretion (ADME), declines in ADME functions of organs with aging, injury, and disease influence the safety of medications [4–6]. In daily clinical practice, multi-medication therapies are used for patients with comorbidities or complications. However, we know little about how many ADEs occur in such patients in daily clinical practice, including patients with renal or hepatic dysfunction, except what we learn from clinical trials. Furthermore, the influence of ADEs on in-hospital mortality or on the length of hospital stay (LOS) of patients with organ dysfunction has not been reported.

In our previous Japan Adverse Drug Events (JADE) study, we evaluated the incidence of ADEs among 3459 hospitalized patients and found that 726 patients had 1010 ADEs during hospitalization, and 6.5% of these ADEs were life-threatening [7]. We are interested in how renal and hepatic dysfunction affects the morbidity and mortality of patients with ADEs in daily clinical practice. Therefore, we investigated how inpatients' renal and hepatic function was related to the occurrence of ADEs. We also investigated the influence of ADEs on in-hospital mortality and on LOS, taking renal and hepatic dysfunction into account.

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Materials and methods

Study design and patient population

The JADE study was a prospective cohort study of 3459 patients aged 15 years or older who were admitted to three tertiary-care hospitals in Japan from January to June 2004. These patients were admitted to 15 medical and surgical wards and three intensive care units in these hospitals [7]. Patients were followed until transfer, discharge, or death.

Ethics approval and consent to participants

The study protocol complied with the Declaration of Helsinki and the guidelines for epidemiological studies issued by the Ministry of Health, Labour, and Welfare in Japan. The institutional review boards of the three participating hospitals (St. Luke's International Hospital, Rakuwakai Otowa Hospital, and Aso Iizuka Hospital) and the Ethics Committee of the Kyoto University Graduate School of Medicine approved the study (E-15). Informed consent was waived because all data were collected in daily clinical practice. This waiver was approved by the institutional review boards.

Data collection and review process

The data collection method was based on that described in a previous report [2]. An ADE was defined as any unintended injury related to medication usage, regardless of existing errors [2, 8]. In the first step, trained research assistants reviewed all practice data (such as medical charts, laboratories, prescription data, incident reports, and prescription queries). They also collected the patient characteristics. Comorbidity in the patients was quantified using the Charlson Comorbidity Index [9].

In the second step, two independent physician reviewers evaluated and classified all data collected by the research assistants as either ADEs or exclusion.

Interrater reliabilities were assessed using κ statistics. The κ scores regarding presence of an ADE between reviewers were 0.75 (ADE vs. potential ADE or exclude) and 0.77 (exclude vs. ADE or potential ADE). The κ for preventability was 0.86 (preventable vs. nonpreventable), whereas κ scores for severity were 0.31 (life-threatening vs. serious or significant) and 0.64 (significant vs. serious or life-threatening) [1].

Renal and hepatic dysfunction

Laboratory data were collected on admission. We calculated the estimated glomerular filtration rate (eGFR) from serum creatinine on admission and divided the patients into the following three categories according to the Japanese CKD guideline [10]. We considered those with eGFR ≥60 mL/min/1.73 mm as having normal renal function, those with ≥30 and <60 mL/min/1.73 mm as having moderate dysfunction, and those with <30 mL/min/1.73 mm as having severe dysfunction.

We used total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma glutamyltransferase (GGTP) as measurements of hepatic function. We defined hepatic dysfunction as having at least one of the four laboratory data points of the hepatic function data beyond a cutoff value. Cutoff values were set from the classification criteria for the seriousness of adverse drug reactions to medications, developed by the Ministry of Health and Welfare in Japan [11]: total bilirubin ≥3.0 mg/dL, AST ≥100 IU/L, ALT ≥100 IU/L, GGTP ≥105 IU/L (male), and GGTP ≥45 IU/L (female).

Statistical analyses

Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range), and categorical variables are shown as numbers and percentages. Relationships between patient's demographic data and ADEs were assessed using the Wilcoxon rank-sum test when the data were continuous and the χ^2 test when the demographic data were categorical. We compared the occurrence of ADEs between patients with and without renal dysfunction, and patients with and without hepatic dysfunction. We compared the occurrence of ADEs between patients with less than five medications on admission and those with five or more medications on admission, and counterpart stratified the test by renal and hepatic dysfunction. We divided the number of medications used into two categories (<5 and ≥5) based on our previous report from the JADE study [7].

We compared LOS and in-hospital mortality between those with ADEs and those without ADEs, stratified by renal or hepatic dysfunction. We also conducted sensitivity analyses excluding the patients who died within 2 days after admission because such patients showed renal or hepatic dysfunction on admission and their abnormal laboratory data and poor prognosis were not associated with ADEs or longer LOS. We finally developed a logistic regression model to assess the effect of renal and hepatic dysfunction on in-hospital mortality, adjusting for age, presence of ADEs, and the number of medications used on admission in the sensitivity analysis cohort. Two-tailed p-values <0.05 were considered statistically significant.

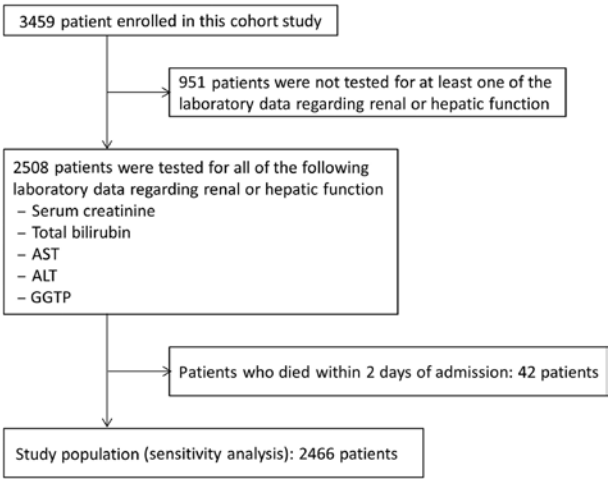

Figure 1: Flowchart of patients.

Table 1: Characteristics and demographics of patients on admission.

Characteristics	Total (n = 2508)	With ADEs (n = 546)	Without ADEs (n = 1962)	p-Value
Age, years, mean ± SD	66.1 ± 16.9	70.3 ± 14.1	64.9 ± 17.4	<0.0001
Men, n (%)	1441 (58)	309 (57)	1132 (58)	0.6
Body mass index, mean ± SD	22.3 ± 4.0	21.4 ± 4.0	22.5 ± 3.9	<0.0001
Wards, n (%)				0.001
Surgical	1132 (45)	261 (48)	871 (44)	
Medical	1022 (41)	233 (43)	789 (40)	
ICUs	354 (14)	52 (10)	302 (15)	
Charlson index score, median (25%–75%)	3 (1–5)	3 (1–5)	2 (1–5)	<0.0001
SBP (mmHg), mean ± SD	131.8 ± 24.3	133.0 ± 25.9	131.4 ± 23.9	0.4
DBP (mmHg), mean ± SD	73.4 ± 14.1	73.7 ± 13.6	73.3 ± 14.2	0.9
Renal function, n (%)				0.01
Normal renal function	1664 (66)	336 (62)	1328 (68)	
Moderate renal dysfunction	584 (23)	152 (28)	432 (22)	
Severe renal dysfunction	260 (10)	58 (11)	202 (10)	
Hepatic function, n (%)				0.01
Normal hepatic function	1716 (68)	349 (64)	1367 (70)	
Hepatic dysfunction	792 (32)	197 (36)	595 (30)	
Drug, n (%)				
Antibiotics	797 (32)	188 (34)	609 (31)	0.13
Antitumor agents	63 (3)	12 (2)	51 (3)	0.59
Diuretics	391 (16)	81 (15)	310 (16)	0.58
Antihypertensive	661 (26)	148 (27)	513 (26)	0.65
Antiarrhythmic	57 (2)	12 (2)	45 (2)	0.89
Cardiovascular	466 (19)	98 (18)	368 (19)	0.67
Anticoagulants	279 (11)	58 (11)	221 (11)	0.67
Dyslipidemic agents	142 (6)	30 (5)	112 (6)	0.85
Antidiabetics	287 (11)	67 (12)	220 (11)	0.49
Antiasthmatics	96 (4)	21 (4)	75 (4)	0.98
Peptic ulcer drugs	890 (35)	202 (37)	688 (35)	0.40
Laxatives	427 (17)	110 (20)	317 (16)	0.028
Antidepressants	30 (1)	7 (1)	23 (1)	0.83
Sedatives	955 (38)	225 (41)	730 (37)	0.087
Antipsychotics	149 (6)	44 (8)	105 (5)	0.018
Antiseizure	69 (3)	19 (3)	50 (3)	0.24
Anti-Parkinson's drugs	38 (2)	10 (2)	28 (1)	0.49
Muscle relaxant	70 (3)	17 (3)	53 (3)	0.61
NSAIDs	569 (23)	151 (28)	418 (21)	0.0017
Other analgesics	666 (27)	156 (29)	510 (26)	0.23
Corticosteroids	145 (6)	41 (8)	104 (5)	0.051
Antihistamines	83 (3)	20 (4)	63 (3)	0.60
Electrolytes or fluids	1338 (53)	284 (52)	1054 (54)	0.48
Experimental drugs	1 (0.04)	1 (0.2)	0 (0)	0.058
Others	1547 (62)	342 (63)	1205 (61)	0.60

ICUs, intensive care units; SBP, systolic blood pressure; DBP, diastolic blood pressure; NSAIDs, nonsteroidal antiinflammatory drugs.

We carried out all analyses using the JMP 11.2 software (SAS Institute Inc., Cary, NC, USA).

Results

Laboratory data of both renal and hepatic function were available for 2508 of the 3459 patients enrolled (Figure 1). After excluding 42 patients who died within 2 days who had no ADE, the data of 2466 patients were used in the sensitivity analysis.

Among the 2508 patients, 546 had ADEs. The mean age was significantly higher in patients with ADEs than in those without (70.3 vs. 64.9 years, $p < 0.0001$). The mean Charlson index score was also significantly higher in patients with ADEs (3 vs. 2, $p < 0.0001$), whereas

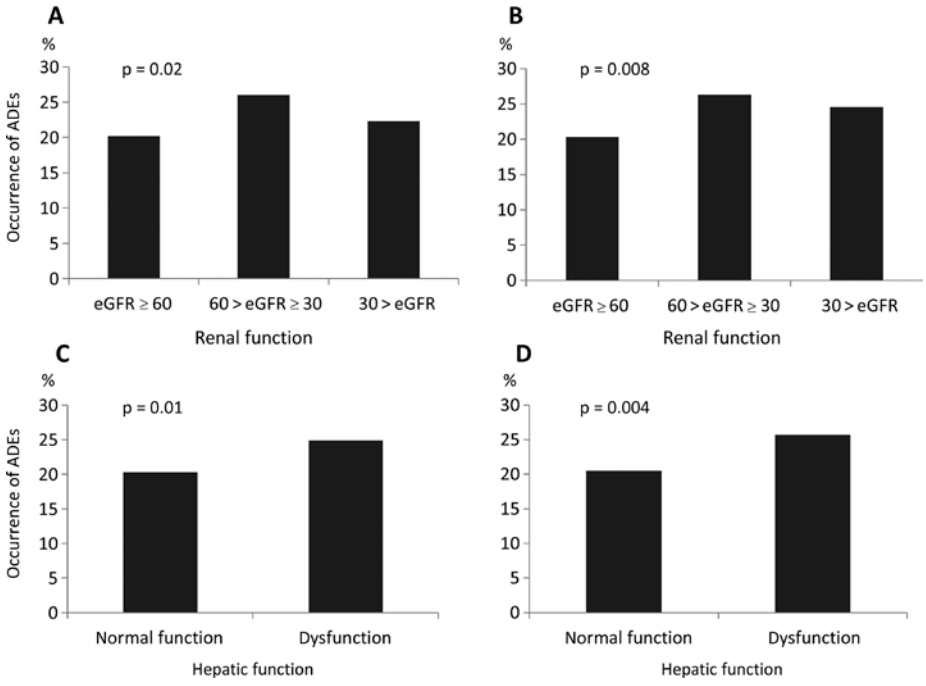

Figure 2: Effect of organ function on ADEs.
(A) The occurrence of ADEs in patients stratified by eGFR category (<30; ≥30 and <60; ≥60 mL/min/1.73 mm). (B) Sensitivity analysis of the occurrence of ADEs in patients in the three eGFR categories. (C) The occurrence of ADEs in patients with normal hepatic function and hepatic dysfunction. (D) Sensitivity analysis of the occurrence of ADEs in patients with normal hepatic function and hepatic function abnormalities.

body mass index was significantly lower (21.4 vs. 22.5, $p < 0.0001$). The categories of renal and hepatic function were also significantly different between the two groups (Table 1).

Effect of renal and hepatic dysfunction on ADEs

The occurrence of ADEs was significantly different among eGFR categories [normal function, 20% (n = 336); moderate dysfunction, 26% (n = 152); and severe dysfunction, 22% (n = 58); p = 0.02] (Figure 2A). The occurrence of ADEs was also significantly different between hepatic function categories [normal function, 20% (n = 349); dysfunction, 25% (n = 197); p = 0.01] (Figure 2C). The sensitivity analyses, excluding patients who died within 2 days, showed similar results [normal renal function, 20%, (n = 336); moderate renal dysfunction, 26% (n = 152); and severe renal dysfunction, 25% (n = 58); p = 0.008; and normal hepatic function, 20% (n = 349); dysfunction, 26% (n = 197); p = 0.004] (Figure 2B and D). Among the 792 patients with hepatic dysfunction, the occurrence of ADEs was higher in the elderly [≥65 years old, 28% (n = 131) vs. 20% (n = 66); p = 0.007].

Effect of number of medications used on ADEs

Among those with normal renal function, ADE occurrence was significantly higher in patients to whom five or more medications were prescribed on admission than in those who were prescribed less than five [25% (n = 143) vs. 18% (n = 193), p = 0.0005] (Figure 3A). However, these effects were not observed among those with moderate or severe renal dysfunction [moderate dysfunction, 25% (n = 60) vs. 27% (n = 92), p = 0.5; severe dysfunction, 23% (n = 35) vs. 22% (n = 23), p = 0.8]. Among those with normal hepatic function, ADE occurrence was also significantly higher in patients to whom five or more medications were prescribed on admission than in those who were prescribed less than five [24% (n = 159) vs. 18% (n = 190), p = 0.007] (Figure 3C). This effect was also not observed among those with hepatic dysfunction. The results of the sensitivity analyses were similar [normal renal function, 25% (n = 143) vs. 18% (n = 193), p = 0.0005; moderate renal dysfunction, 25% (n = 60) vs. 27% (n = 92), p = 0.5; severe renal dysfunction, 24% (n = 35) vs. 25% (n = 23), p = 0.9; and normal hepatic function, 24% (n = 159) vs. 18% (n = 190), p = 0.008; hepatic dysfunction, 27% (n = 79) vs. 25% (n = 118), p = 0.4] (Figure 3B and D).

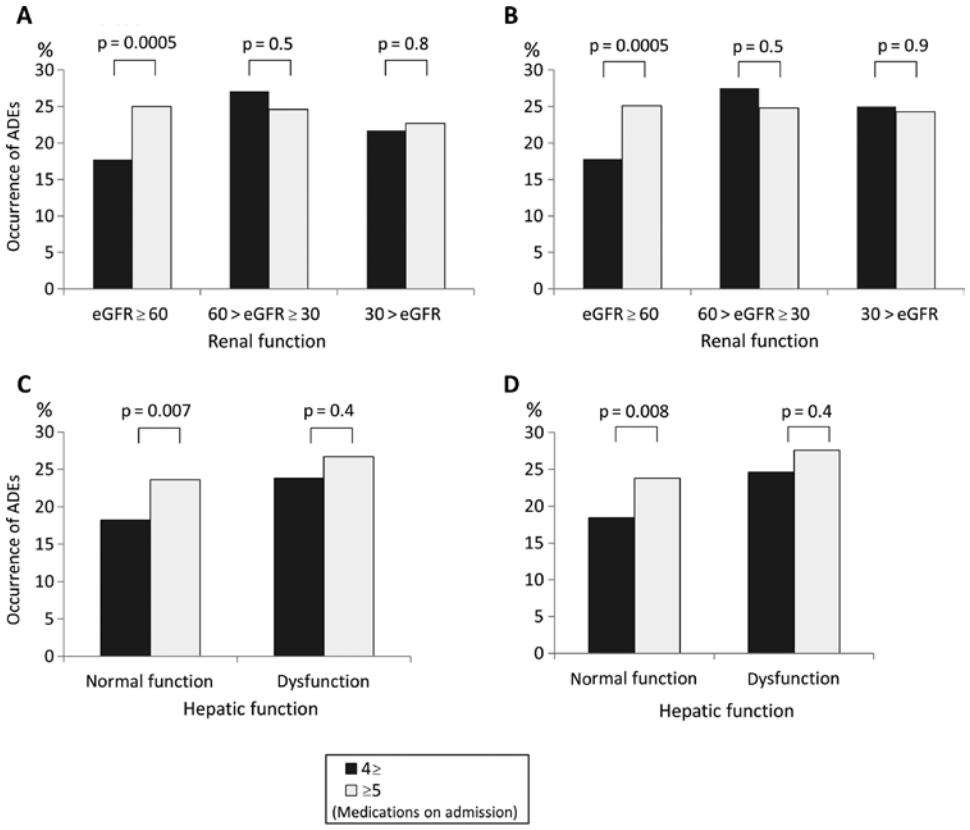

Figure 3: Effect of the number of medications used on ADEs, stratified by organ function.
(A) The occurrence of ADEs in patients in the three eGFR categories (<30; ≥30 and <60; ≥60 mL/min/1.73 mm), stratified by the number of medications used. (B) Sensitivity analysis of the occurrence of ADEs in patient in the three eGFR categories, stratified by the number of medications used. (C)The occurrence of ADEs in patients with normal hepatic function and hepatic dysfunction, stratified by the number of medications used. (D) Sensitivity analysis of the occurrence of ADEs in patients with normal hepatic function and hepatic dysfunction, stratified by the number of medications used. Black bars, the number of medications used is four or less; white bars, the number of medications used is five or more.

Effect of ADEs on LOS

The median LOS of patients with ADEs was longer than that of patients without ADEs, among those with normal renal function (20 vs. 7 days, $p < 0.0001$) and those with renal dysfunction (moderate renal dysfunction, 26 vs. 9 days, $p < 0.0001$; severe renal dysfunction, 22 vs. 6 days, $p < 0.0001$). It was also longer among those with normal hepatic function (21 vs. 7 days, $p < 0.0001$) and those with hepatic dysfunction (23 vs. 8 days, $p < 0.0001$). The results of the sensitivity analyses were similar.

Effect of ADEs on in-hospital mortality

In-hospital mortality was higher in patients with ADEs than in patients without ADEs, among patients with normal renal function and moderate renal dysfunction [normal renal function, 13.7% (n = 46) vs. 3.9% (n = 52), $p < 0.0001$; moderate renal dysfunction, 15.1% (n = 23) vs. 8.3% (n = 36), $p = 0.02$] (Figure 4A). However, these effects were not observed among those with severe renal dysfunction [24.1 (n = 14) vs. 20.8 (n = 42), $p = 0.6$]. In the sensitivity analysis, in-hospital mortality showed the same tendencies in the normal renal function and moderate renal dysfunction groups. However, in this analysis, in-hospital mortality was also higher in patients with ADEs among those with severe renal dysfunction [24.1 (n = 14) vs. 10.1 (n = 18), $p = 0.01$] (Figure 4B). Similarly, in-hospital mortality was higher in patients with ADEs among those with normal hepatic function [13.2 (n = 46) vs. 4.8 (n = 65), $p < 0.0001$] and hepatic dysfunction [18.8% (n = 37) vs. 10.9% (n = 65), $p = 0.006$] (Figure 4C). The hepatic function results of the sensitivity analyses were similar (Figure 4D).

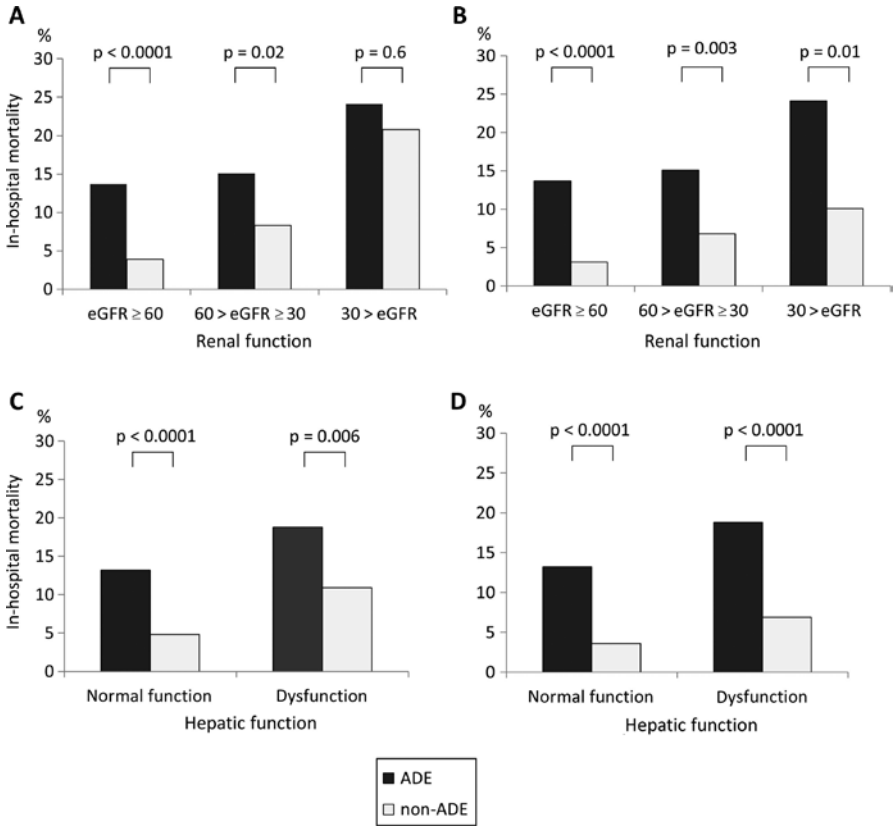

Figure 4: Effect of ADEs on in-hospital mortality, stratified by organ functions.
(A) In-hospital mortality in patients in the three eGFR categories (<30; ≥30 and <60; ≥60 mL/min/1.73 mm), stratified by ADE occurrence. (B) Sensitivity analysis of in-hospital mortality in patients in each eGFR category, stratified by ADE occurrence. (C) In-hospital mortality in patients with normal hepatic function and hepatic dysfunction, stratified by ADE occurrence. (D) Sensitivity analysis of in-hospital mortality in patients with normal hepatic function and hepatic dysfunction, stratified by ADE occurrence.

Effect of renal and hepatic dysfunction on in-hospital mortality

The multivariate logistic regression model showed moderate and severe renal dysfunction were significantly associated with in-hospital mortality [odds ratio (OR) of moderate relative to normal, 1.49 (95% confidence interval, CI, 1.04–2.12); OR of severe relative to normal, 4.12 (95% CI, 2.81–6.02)]. Hepatic dysfunction was also significantly associated with in-hospital mortality (OR, 2.08; 95% CI, 1.55–2.79). The occurrence of ADEs was also independently associated with in-hospital mortality, adjusting

Table 2: Effect of renal and hepatic dysfunction on in-hospital mortality by univariate and multivariate analysis.

Variables	Univariate		Multivariate	
	OR		OR	
	(95% CI)	p-Value	(95% CI)	p-Value
ADEs	2.53 (1.88–3.39)	<0.0001	2.36 (1.74–3.20)	<0.0001
Age ≥65 years	2.05 (1.48–2.83)	<0.0001	1.67 (1.19–2.37)	0.0029
Renal dysfunction (eGFR, mL/min/1.73 mm)				
≥60	1 (reference)		1 (reference)	
≥30 and <60	1.29 (0.94–1.77)	0.12	1.49 (1.04–2.12)	0.029
<30	3.66 (2.61–5.12)	<0.0001	4.12 (2.81–6.02)	<0.0001
Hepatic dysfunction	2.13 (1.61–2.84)	<0.0001	2.08 (1.55–2.79)	<0.0001
No. of medications ≥5	1.34 (0.78–1.38)	0.81	0.83 (0.61–1.12)	0.23

for renal and hepatic dysfunction (OR, 2.36; 95% CI, 1.74–3.20) (Table 2).

Discussion

We found that approximately 30% of unselected inpatients in acute-care hospitals had renal or hepatic dysfunction, and that the risk of ADEs in such patients was significantly higher than in patients with normal organ function. We also found that the variables associated with increased occurrence of ADEs, such as being elderly, having renal dysfunction, and having hepatic dysfunction, were also independently associated with in-hospital mortality.

However, the occurrence of ADEs with severe renal dysfunction was smaller than the occurrence with moderate renal dysfunction. In-hospital mortality was significantly associated with renal dysfunction. Therefore, more patients with renal dysfunction would die before experiencing ADEs during the hospital stay. Indeed, the occurrence of ADEs with severe renal dysfunction increased when patients who died within 2 days were excluded.

Our findings were consistent with those from a previous study, which showed that a substantial proportion (7.5%–10.4%) of patients admitted to acute-care hospitals experienced ADEs, with some of them being fatal [12].

Prevention of ADEs is expected to improve the prognosis of patients. In the United States, ADEs contribute to as many as 140,000 deaths annually, occurring in about 1 of 16 hospitalized patients. An estimated 28% to 56% of ADEs are preventable, and most preventable ADEs are due to errors during prescription [12]. A UK study showed that 12% of all primary-care patients may be affected by a prescribing or monitoring error over the course of a year, increasing to 38% in those aged 75 years and older and 30% in patients receiving five or more drugs during a 12-month period. Overall, about 5% of prescriptions are believed to have prescribing errors [13]. The WHO has provided a list of 10 key actions that are likely to have the most impact on improving safety in primary care, and one of them is to focus on those at a higher risk of safety incidents [14]. Our study showed that ADEs occurred significantly more in patients with organ dysfunction. Thus, intensive monitoring of such patients would contribute to reducing the incidence of ADEs, morbidity, and mortality.

In patients with normal renal or hepatic function in this study, the occurrence of ADEs increased when the number of medications increased. However, this tendency was not observed in patients with renal or hepatic dysfunction. Field et al. [15] reported that the risk of ADEs increased when the number of regularly scheduled medications was more than five in patients with normal renal and hepatic function, and our results were consistent with this report. Generally, drugs and their metabolites are excreted in the urine after polarization by a drug metabolism process in the liver [5]. If patients have hepatic or renal dysfunction, then this metabolism or excretion process has deteriorated. The relationship between the number of medications and occurrence of ADEs was not observed in patients with renal or hepatic dysfunction because of the decreased metabolism and excretion function. Even with only a few drugs administered, the blood concentration of these drugs or their metabolites increases causing enhanced drug sensitivity in patients with renal or hepatic dysfunction [16–22]. We suggested that the risk of ADEs depends on the number of medications in patients with normal metabolism, whereas the risk of ADEs was high even with a small number of medications in patients with decreased metabolism.

The efficiency of renal and hepatic function changes with age [23–25], and mean age on admission was 70 years in patients with ADEs in our study. Budnitz et al. [26] reported in a US study that there were an estimated 99,628 emergent hospitalizations for ADEs in adults aged 65 years or older each year from 2007 to 2009. Nearly half of these hospitalizations were reported for adults aged 80 years or older, and nearly two thirds of those were due to unintentional overdoses. In the same study, two thirds of the ADEs involved drugs such as warfarin, insulin, oral antiplatelet agents, and oral hypoglycemic agents. More caution during prescription is needed because many medications could cause renal or hepatic dysfunction [27–31]. In contrast, Dreischulte et al. [32] reported in a Scotland study that a complex intervention combining professional education, informatics, and financial incentives reduced the rate of high-risk prescribing of antiplatelet medications and nonsteroidal antiinflammatory drugs. The proper use and dose of medications are more important for elderly patients with renal or hepatic dysfunction because our results indicated that being elderly and having renal or hepatic dysfunction and ADEs were independently associated with in-hospital mortality. Furthermore, monitoring of renal and hepatic function should be approached with more attention in cases of multiple medication therapy.

Several limitations must be addressed regarding this study. First, the number of all medications were not available during the hospitalization. The changes in laboratory data after admission were also not assessed. Although the

primary purpose of this study was to estimate the risk of ADEs and in-hospital mortality based on the renal and hepatic functions on admission, the changes in medication use and laboratory data could be incorporated to risk stratification. Second, we also did not assess the established indicators of hepatic function, which are widely used for the prognosis of liver disease, such as the Child–Pugh score [33]. Therefore, the effect of renal and hepatic function on the occurrence of ADEs might be different if we used different indicators. Third, we did not consider pharmacogenomics or pharmacokinetic/pharmacodynamic studies to estimate the risks of ADEs in this study because such tests were not used in all patients in daily practice. We focused on the risk of ADEs based on renal and hepatic function, which are measured in all patients on admission. However, the risk stratification ability should be improved if we used such tests in the future. Finally, the JADE study only enrolled Japanese patients, and the study was conducted in 2004, with data that seem relatively old. To generalize our results globally, we need to study the effect of renal and hepatic function on the occurrence of ADEs in other countries to evaluate their effects among different ethnic groups and also in different healthcare systems, which can affect decision-making by healthcare professionals. However, as the medications used in this study have not been changed for decades, our findings and their clinical implication should be considered relevant in the present.

Conclusions

We found that renal and hepatic dysfunction increased the occurrence of ADEs, and that ADEs were associated with longer LOS and higher mortality in patients with both normal and decreased renal or hepatic function. Therefore, the appropriate and careful use of medication should be promoted, especially in patients with renal or hepatic dysfunction. Systems to confirm the necessity of organ function tests depending on the medications that a patient is taking, and to increase the timely identification and interception of ADEs according to renal or hepatic function, should be implemented to ensure the safer use of medication.

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ORIGINAL ARTICLE

Improving the assessment of adverse drug reactions using the Naranjo Algorithm in daily practice: The Japan Adverse Drug Events Study

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Abstract

It is difficult to determine adverse drug reactions (ADRs) in daily complicated clinical practice in which many kinds of drugs are prescribed. We evaluated how well the Naranjo Algorithm (NA) categorized ADRs among suspected ADRs. The Japan Adverse Drug Events (JADE) study was a prospective cohort study of 3459 inpatients. After all suspected ADRs were reported from research assistants, a single physician reviewer independently assigned an NA score to each. After all NA score of suspected ADRs were scored, two physician reviewers discussed and determined ADRs based on the literature. We investigated the sensitivity and specificity of NA and each component to categorize ADRs among suspected ADRs. A total of 1579 suspected ADRs were reported in 962 patients. Physician reviewers determined 997 ADRs. The percentage of ADRs was 94% if the total NA score reached 5. The modified NA consisted of 5 components that showed high classification abilities; its area under the curve (AUC) was 0.92 for categorizing ADRs, the same as the original. When we set the total NA score cut-off value to 5, specificity was 0.95 and sensitivity was 0.59. When we reclassified NA components as binary variables, the specificity increased to 0.98 with a cut-off value of 4 and yielded an AUC of 0.93. In conclusion, we showed that both NA and modified NA could categorize ADRs among suspected ADRs with a high likelihood in daily clinical practice.

KEYWORDS
adverse drug reactions, categorization, daily practice, JADE study, modification, Naranjo Algorithm, patient safety, pharmacovigilance, sensitivity, specificity

1 | INTRODUCTION

Discriminating adverse drug events (ADRs) from various symptoms in daily practice is important in order for physicians to take action to mitigate the adverseness and prevent recurrence. However, patients are usually treated with many kinds of drugs, which make it difficult to identify an ADR in daily practice. A tool to categorize ADRs

Abbreviations: ADRs, adverse drug reactions; AUC, area under the curve; JADE, The Japan Adverse Drug Events; NA, Naranjo Algorithm; ROC, receiver operating characteristic.

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among complicated suspected symptoms could be useful for healthcare professionals to take action proactively as well as to confirm the probability of ADRs retrospectively.

Naranjo et al proposed a tool to evaluate the probability of true ADRs from suspected ADRs,[1,2] and it has been widely used as the Naranjo Algorithm (NA).[3-6] In addition to the NA, several assessment tools have been developed, such as the Liverpool adverse drug reaction causality assessment tool[7] and the French Causality Assessment Method.[8] These tools are used to evaluate the probability of an ADR rather than to screen ADRs from suspected ADRs prospectively to take action. While the NA is a traditional tool, it consists of 10 components, and it is complicated to calculate the total score and would require time to utilize it in a daily clinical setting. To save time and resources, a convenient tool to categorize ADRs with high specificity is needed.

We recently conducted the Japan Adverse Drug Events (JADE) study, which evaluated the incidence of ADRs and medication errors among Japanese hospitalized inpatients.[9-14] In the present study, we evaluated the usefulness of the NA to categorize ADRs among suspected ADRs using the JADE database and tried to modify it into a convenient tool to use in daily clinical practice.

2 | MATERIALS AND METHODS

2.1 | Study design and patient population

The JADE study was a multicenter prospective cohort study that included 3459 inpatients aged ≥15 years. The study site was three urban tertiary care hospitals in Japan, patients admitted at 15 randomly selected medical and surgical wards as well as three intensive care units from January through June 2004 were eligible for this study.[9] The institutional review boards of the three participating hospitals approved the study. Informed consent was waived because all data were collected in daily practice.

2.2 | Naranjo Algorithm

The NA consists of 10 components assessing the likelihood of ADRs.[1,2] Each component is scored from −1 to +2 based on the findings of each event, including (1) previous conclusive reports, (2) time course, (3) improvement after withdrawal or treatment, (4) re-emergence after re-challenge, (5) other causative conditions of symptoms, (6) response to placebo if used, (7) evidence in blood of toxicity, (8) dose response, (9) similar reactions before, and (10) other objective evidence.

2.3 | Data collection and review process

Research assistants, who were trained nurses or nursing students, reviewed all medical charts, along with laboratory results, incident reports, and prescription queries by pharmacists with the standardized form daily. They reported any suspected ADRs that might be potential ADRs in a standard manner.[15] After all suspected ADRs were reported from research assistants, a single physician reviewer independently assigned an NA score to each suspected ADR. After all NA score of suspected ADRs were scored, two independent physician reviewers evaluated all suspected ADRs and classified them as confirmed ADRs or not. If discordance happened, such discordance was resolved through discussion to reach consensus.

2.4 | Statistical analyses

A continuous variable is presented as the mean ± standard deviation (SD) and categorical variables are shown as numbers and percentages. We expressed the distribution of NA scores in each component as the percentage of confirmed ADRs among suspected ADRs for each score in each component. We evaluated the percentage of confirmed ADRs among suspected ADRs for each total NA score. ADRs which are confirmed by physician reviewers are considered as true positive. All suspected ADRs were categorized as positive or negative based on the NA score; then sensitivity and specificity were calculated by these figures. We constructed a receiver operating characteristic (ROC) curve for the summed score of all and selected NA components to compare the categorization abilities of original and modified NA scores. To simplify the NA for convenient use, we reclassified NA components as binary variables. For example, an NA component that had three possible scores, such as +2, 0, and −1 or +1, 0, and 1, were converted to +1 and 0 in which the positive score was converted to +1 and the 0 and negative scores were summarized as 0. We carried out all analyses using JMP 11.2 (SAS Institute Inc., Cary, NC, USA) software.

3 | RESULTS

There were 1579 suspected ADRs occurring in 962 patients from among 3459 patients enrolled (Figure 1). Physician reviewers finally concluded that 997 actual ADRs occurred from among the suspected ADRs. Among the 962 patients with NA scores, 517 (54%) were men and the mean age was 70 (SD 15) years. The medical and surgical wards and the ICUs admitted 437 (45%), 410 (43%), and 115 (12%) patients, respectively. Comorbidities based on the Charlson index are summarized in Table 1. Medications that were the most frequently associated with ADRs were electrolytes or fluids (n = 623, 62%), followed by antibiotics (n = 569, 57%) and peptic ulcer drugs (n = 463, 46%) (Table 2).

3.1 | Distribution of NA score and percentage of ADRs by each component

NA components 6 through 10 (response to placebo if used, evidence in blood of toxicity, dose response, similar reactions before, and other objective evidence) classified more than 95% of suspected ADRs with a specific score; in which 99.8% (n = 1576) of suspected ADRs were classified with a score 0 (do not know) for component 6, and 99.9% of suspected ADRs were classified with a score 0 (no or do not know) for component 7. Thus, components 6 through 10 did

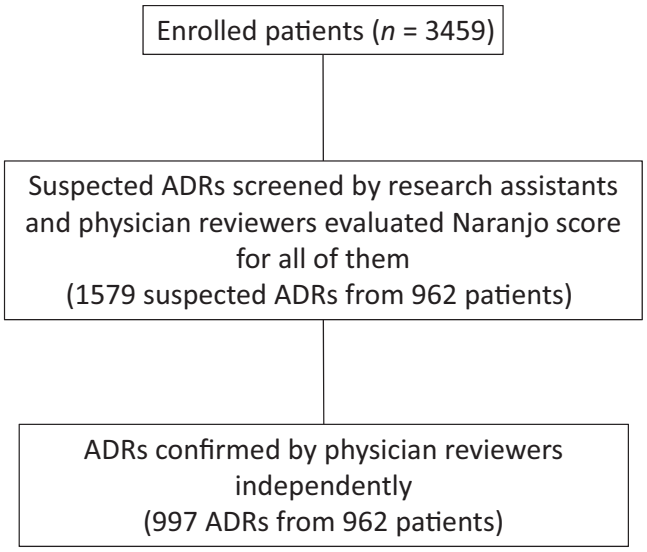

FIGURE 1 Evaluation process for adverse drug events (ADRs). ADRs were evaluated using 3 steps. Research assistants suggested suspected ADRs from potential drug-related incidents. A physician reviewer scored each suspected ADR independently using the NA. Two physician reviewers identified ADRs based on consensus of an expert panel

not show sufficient categorization in identifying ADRs in this cohort. On the other hand, components 1 through 5 (previous conclusive report, time course, improvement after withdrawal or treatment, re-emergence after re-challenge, and other causative conditions of symptoms) showed good categorization in identifying ADRs from among suspected ADRs for each component; in which 64% (n = 1002) of suspected ADRs were classified with a + 1 score (yes) and 37% (n = 577) of suspected ADRs were classified with a 0 score (no or do not know) for component 1 (Table 3).

TABLE 1 Characteristics and demographics of patients on admission

Characteristic	Mean ± SD or n (%) n = 962
Age (years)	70.0 ± 14.8
Male sex	517 (54)
Race (Japanese)	957 (99.5)
Admitting ward	
Medical	437 (45)
Surgical	410 (43)
Intensive care units	115 (12)
Comorbidity	
Myocardial infarction	67 (7)
Heart failure	141 (15)
Peripheral vascular disease	54 (6)
Cerebrovascular disease	136 (14)
Dementia	143 (15)
Chronic obstructive pulmonary disease	122 (13)
Rheumatologic	38 (4)
Peptic ulcer	247 (26)
Liver diseases	177 (18.4)
Diabetes	163 (16.9)
Chronic kidney disease	61 (6)
Any tumor	377 (39.2)

Most parameters are duplicated to a certain degree, as many patients experienced multiple medical events.

TABLE 2 Medications suspected to induce adverse drug reactions (ADRs)

Medication	n (%) n = 997
Electrolytes or fluids	623 (62)
Antibiotics	569 (57)
Peptic ulcer drugs	463 (46)
Sedatives	360 (36)
Antihypertensive	302 (30)
Laxatives	254 (25)
Diuretics	221 (22)
Cardiovascular	202 (20)
NSAIDs	194 (19)
Anticoagulants	170 (17)
Antidiabetics	139 (14)
Antipsychotics	119 (12)
Dyslipidemic agents	73 (7)
Analgesics	42 (4)

NSAIDs, nonsteroidal anti-inflammatory drugs.

Each NA component 1 to 5 had relatively high sensitivity or specificity for categorizing ADRs among suspected ADRs. With component 1, 86% (n = 866) of suspected ADRs were confirmed as ADRs among 1002 suspected ADRs assigned a + 1 score (Yes), and 23% (n = 131) of suspected ADRs were confirmed as ADRs among 577 suspected ADRs assigned a 0 score (No/Do not know) (Figure 2). Since the NA has a "Do not know" classification, we simply could not calculate specificity. When we classified "do not know" as "no", the sensitivity was 0.87 and specificity was 0.77 for component 1. Similarly, the approximate sensitivity and specificity were 0.99 and 0.68, respectively, for component 2; 0.31 and 0.97, respectively, for component 3; 0.27 and 0.93, respectively, for component 4; and 0.71 and 0.91, respectively, for component 5.

3.2 | Relationship between total NA score and ADRs percentage of suspected ADRs

The total NA score calculated for each suspected ADR ranged from −2 to 11. The most frequent total NA score was 0 (n=403) followed by 5 (n=280). The percentage of ADRs was 56% if the total NA score was 1, and it gradually increased to 94% if the total NA score reached 5 (Figure 3). We did not show the total NA scores of −2 and −1 since only 2 and 0 suspected ADRs, respectively, were assigned these scores.

TABLE 3 Distribution of the Naranjo Algorithm (NA) score for each component

	Component	Score			
		+2	+1	0	−1
1	Are there previous conclusive reports on this reaction?	—	1002 (64)	577 (37)	—
2	Did the adverse event appear after the suspected drug was administered?	1172 (74)	—	400 (25)	7 (0.4)
3	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	—	322 (20)	1257 (80)	—
4	Did the adverse reaction reappear when the drug was readministered?	309 (20)	—	1040 (66)	230 (15)
5	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	761 (48)	—	422 (27)	396 (25)
6	Did the reaction reappear when a placebo was given?	—	3 (0.2)	1576 (99.8)	0 (0)
7	Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	—	2 (0.1)	1577 (99.9)	—
8	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	—	24 (2)	1555 (98)	—
9	Did the patient have a similar reaction on the same or similar drugs in any previous exposure?	—	35 (2)	1544 (98)	—
10	Was the adverse event confirmed by any objective evidence?	—	53 (3)	1526 (97)	—

Data expressed as n (%).

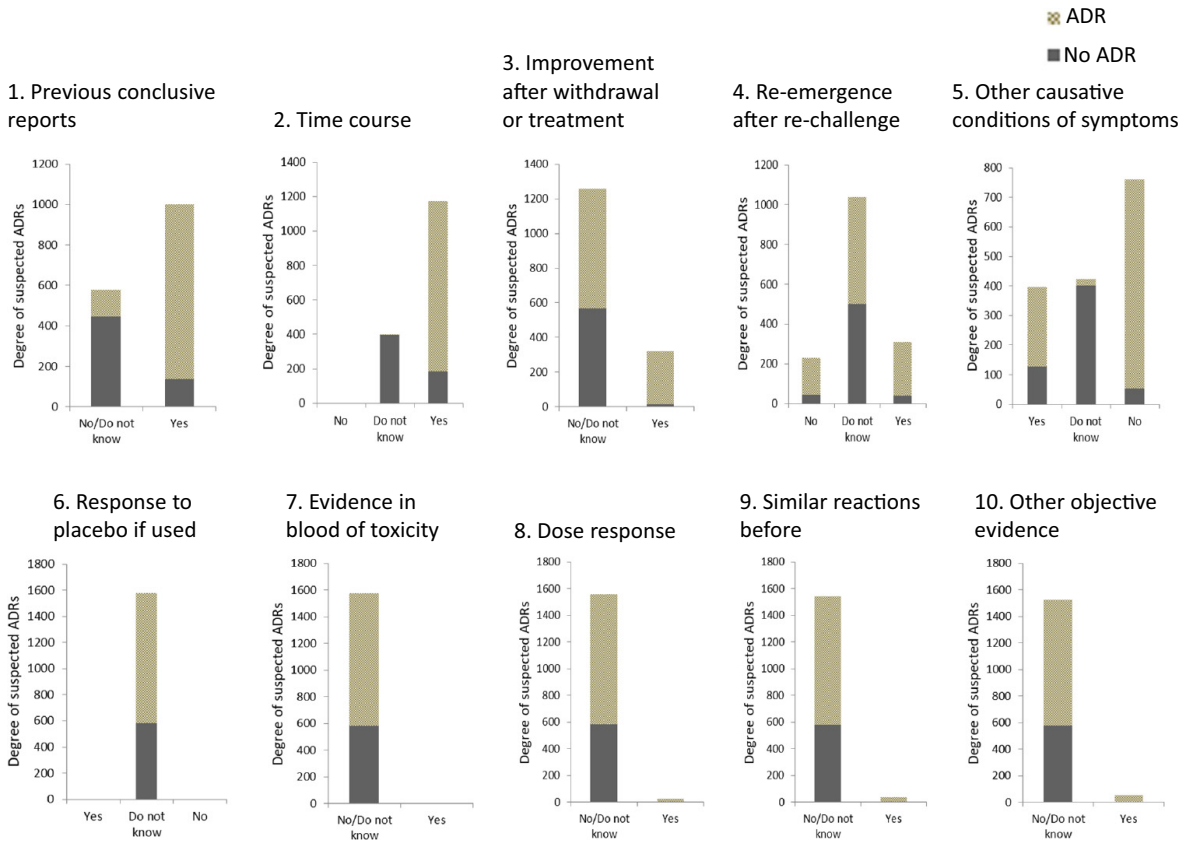

FIGURE 2 Distribution of adverse drug reactions (ADRs) by each Naranjo Algorithm (NA) component. The distribution of ADRs identified by physician reviewers for scored suspected ADRs by each NA component is shown. A total of 10 components, each consisting of 2 or 3 classifications were evaluated

3.3 | Sensitivity and specificity of the NA to determine ADRs

The area under the curve (AUC) to confirm ADRs was 0.92 (95% confidence interval [CI]: 0.91-0.94) based on the total NA sore; the specificity was 0.94 and the sensitivity was 0.61 if the cut-off value was set at 5 (Figure 4A). Since more than 97% of suspected ADRs were assigned a score of 0 for components 6 through 10, we considered that these components were not useful in the real-world setting. We generated a modified NA that consisted of components 1

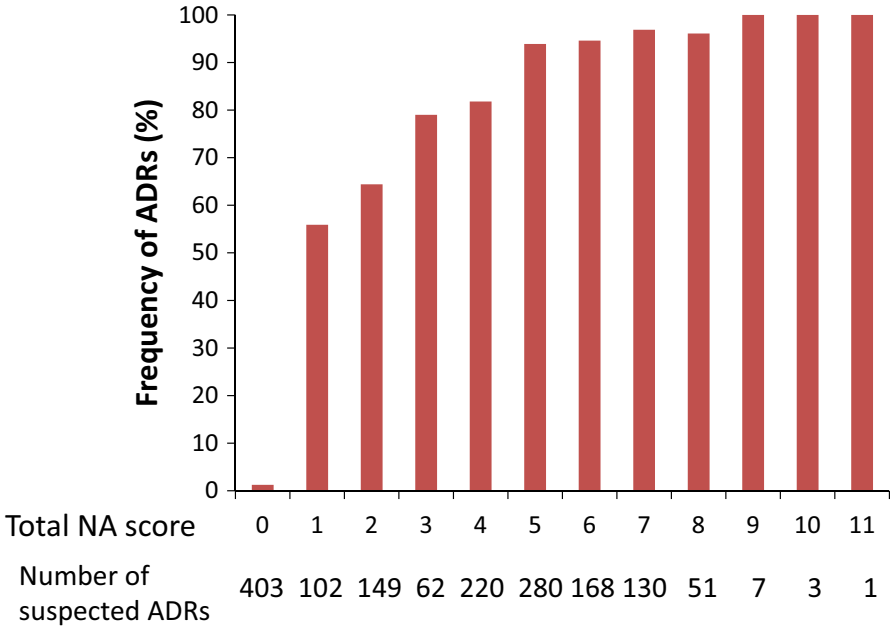

FIGURE 3 Relationship between the total Naranjo Algorithm (NA) score and the percentage of identified adverse drug events (ADRs) among suspected ADRs. The percentage of confirmed ADRs among suspected ADRs are expressed for each total NA score (0 through 11)

through 5. This modified NA confirmed ADRs with an AUC of 0.92 (95% CI: 0.91-0.94), which was the same AUC as the original NA (Figure 4B). If the cut-off value was set at 5, the specificity was 0.95 and sensitivity was 0.59. In the modified NA, we reclassified NA components 2, 4, and 5 into binary variables, which increased the specificity to 0.98 and sensitivity of 0.34 with an AUC of 0.93 (95% CI: 0.91-0.94) if the cut-off value was set at 4 (Figure 4C). We further modified the NA to consist of components 2 through 5 as binary variables. This simplest NA confirmed ADRs with an AUC of 0.92 (95% CI: 0.90-0.93) and showed a specificity of 0.97 and sensitivity of 0.40 if the cut-off value was set at 3 (Table 4, Figure 4D).

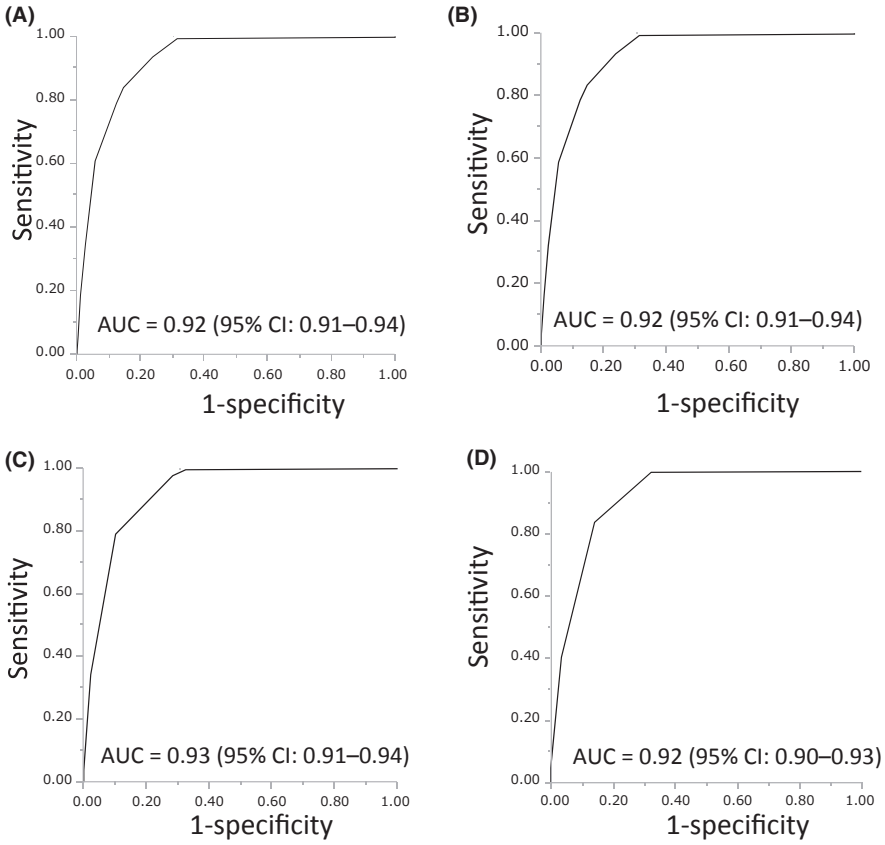

FIGURE 4 Receiver operating characteristic curve for adverse drug events (ADRs) and total Naranjo Algorithm (NA) score. A, The AUC for the sum of all NA components. B, The AUC for selected NA components (1-5). C, The AUC for selected NA components (1-5) converted to binary scores (0 or 1). D, The AUC for selected NA components (2-5) converted to binary scores (0 or 1)

TABLE 4 Modified Naranjo Algorithm (NA)

	Component	Score	
		Yes	No/Do not know
2	Did the adverse event appear after the suspected drug was administered?	+1	0
3	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0
4	Did the adverse reaction reappear when the drug was readministered?	+1	0
5	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	0	+1

4 | DISCUSSION

We showed that the NA was able to categorize ADRs among suspected ADRs efficiently in daily clinical practice using the large-scale JADE database,[9] which was independent with a consensus panel by physicians' reviewers. While each NA component showed relatively high sensitivity or specificity, we evaluated the sensitivity or specificity for the total NA score, since healthcare professionals usually make a decision from multiple factors in the actual clinical setting. We also showed that the modified NA, consisting of components 1 through 5, also effectively categorized ADRs with a high likelihood. We further modified the NA to include all binary scores for components 1 through 5 and found that this algorithm determined ADRs with high likelihood, also similar to the original. In addition, we removed component 1 because this component required sufficient knowledge of ADRs for each suspected drug. We considered that the modified NA with binary scores for components 2 through 5 was the most reasonable in terms of the practical use in daily clinical practice and its effectiveness in determining ADRs with a high likelihood, similar to the original index and all of the other modified NAs.

In previous studies, the NA was utilized retrospectively to evaluate the probabilities of ADRs in a specific case or cohort.[3-6] In this study, however, we showed that the NA had high predictive accuracy for determining true ADRs among suspected ADRs, which could contribute to safety monitoring activities by healthcare professionals or pharmaceutical manufacturers. If the modified NA score is simultaneously reported with a suspected ADR, a health authority or pharmaceutical manufacturers could evaluate the suspected ADR more easily and quickly and could allocate time and resources more effectively. For example, pharmaceutical manufacturers could start an intensive survey giving priority to a suspected ADR with a high modified NA score. Additionally, healthcare professionals could start preclinical studies to clarify the mechanism of ADRs focusing on a high modified NA score. Thus, the modified NA score could help healthcare professionals or pharmaceutical manufacturers take their own action in preventing ADRs as early as possible before health authorities issue a warning or guidance.

NA was reported to show poor performance for causality assessment of hepatic adverse reactions.[16,17] On the other hand, NA and modified NA were able to categorize ADRs among suspected ADRs including hepatic adverse reactions in the current study. However, the number of hepatic adverse reactions was limited in the current study, the reliability to assess such hepatic adverse reactions was uncertain. Further studies which address the accuracy of NA and modified NA against hepatic adverse reaction should be considered.

Other than the NA, Gallagher et al reported the usefulness of the Liverpool adverse drug reaction causality assessment tool.[7] Although this tool also tried to simplify the NA and increase its credibility, their study had different objectives. It takes time to evaluate one case and provide an outcome (possible, probable, or definite) using the probability tree in the Liverpool tool. Additionally, this tool does not provide any score to be evaluated for sensitivity and specificity, similar to the NA. Also WHO-UMC causality assessment could be another simple tool to categorize ADR.[18] While this tool takes number of assessment criteria into consideration to categorize ADRs and each assessment criteria are similar to NA, it does not provide any score to be evaluated for sensitivity and specificity as well. Thus, there have been few reports proposing a tool that could be used to take action to mitigate adverseness and to prevent recurrence proactively rather than merely confirming the probability of ADRs retrospectively. We think our modified NA will not jeopardize the spontaneous ADR reporting but increase the awareness of ADR reporting with simple tool. It is still challenge for medical professionals to report suspected ADRs spontaneously because the importance of ADR reporting could not be understood well and medical professionals do not have an effective trigger tool to report ADRs. We are convinced that simple ADR assessment tools including our modified NA can introduce more frequent ADR reporting among medical professionals and can be used as a trigger tool to report ADRs.

Our study has several limitations. First, the JADE study only enrolled inpatients. Therefore, the modified NA score in this study might not be applicable in outpatients. Pharmacovigilance for inpatient should be different from usual pharmacovigilance situation of spontaneous reporting. Further studies are needed to clarify whether our findings could be applicable in outpatient settings and to generalize the modified NA for use in a pharmacovigilance system. Second, we removed components 6-10 in the modified NA model. For drugs in which the blood level should be known, such as vancomycin or theophylline, component 7 could be useful for detecting ADRs. However, only 2 cases were given a score of +1 for that component in this study, which shows that measuring blood levels of suspected drugs is not frequent in daily clinical practice. Third, the same independent physician reviewer classified the ADR and scored NA at different times, which might have led to a connection between ADR classification and NA scoring and subsequently to misclassification of the NA based on the reviewer's background or knowledge. Fourth, the JADE study only enrolled Japanese patients. To generalize the results globally, we need to study the modified NA in other countries to evaluate its ability to categorize ADRs among various races

and in different healthcare systems, which affect decision-making by healthcare professionals. Fifth, the JADE study was conducted in 2004 and the data used seemed relatively old. However, NA was developed in 1981 and still used for clinical settings. The drug used in this study and spontaneous ADR reporting system has not been changed for decades. Thus, the findings and clinical implication of this study should be valid at present time. Finally, we focused on the most suspected drug among all drugs administered when symptoms occurred in this study. Therefore, we could not exclude the possibility of synergistic effects of multiple drugs and drug-drug interaction.

In conclusion, we assessed the categorization abilities of the original and modified NAs in daily practice and found that the modified NA could be easily used to categorize actual ADRs among suspected ADRs with high predictive accuracy. Therefore, use of the modified NA could help to save time and resources and categorize ADRs more effectively and promptly in daily clinical practice. Additionally, utilizing this tool for a pharmacovigilance system could be useful to enable professionals take prompt action in developing a strategy to prevent and mitigate the adverseness of ADRs.

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DISCLOSURES

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島根県中病医誌 43
17頁 ～ 22頁

外来患者への適切な投薬指示のための臨床決断支援システム

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概　要：【背景・目的】島根県立中央病院の臨床決断支援システムの１つとして入院患者における腎機能別の推奨投与のシステムを開発したところ有用であった。同様のシステムを外来患者に導入し、有効性を評価した。

【方法】既存の入院患者向けシステムでは、入院患者の腎機能を自動計算し推奨投与量を画面上で医師に示したうえで、医師が最終的に用量を選択できる。同システムを元に、腎機能に基づいた抗微生物薬処方の臨床決断支援システムを外来患者用に開発した。2017年10月よりシステムを導入し、2018年９月時点では実際にカルテ画面には出さず介入前のバックグラウンドの状況で稼働中である。開始から2018年７月までの10か月間の抗微生物薬処方内容を調査し、システム本稼働後の実際の効果を予測した。

【結果】腎機能で調整が必要な薬剤は薬品単位で35,594件であった。腎機能が測定されていなかった患者における処方は、5,675件（16％）であった。腎機能測定されていた場合に、腎機能から計算された適切な処方は27,852件（78％）で、適切でないと判断された処方は、2,067件（６％）だった。

【結語】システム本稼働後は腎機能の測定の増加と適切でない処方の減少が期待される。

索引用語：決断支援システム、腎機能、抗微生物薬、抗微生物薬適正使用

Clinical decision support system for appropriate medication orders in outpatient service

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Abstract：**Objectives;** We had developed a clinical decision support system, which enabled physicians to order any medication with recommended doses based on the updated renal function of each inpatient at Shimane Prefectural Central Hospital. We launched the same system into outpatient settings, and evaluated them.

Methods; We developed the clinical decision support system which automatically recommended appropriate doses for any medication which needed to be adjusted for renal function for inpatients. Recommended doses were displayed on the screen for inpatients, the physician could finally select the clinical dose. Since October 2017, we installed the system in outpatients, but the recommended doses were not displayed on the screen and ran in the background to measure the baseline data. We measured the antimicrobial prescription contents for 10 months until July 2018 to predict the actual effect after system

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operation.

Results; We obtained 35,594 drugs regulated by renal function orders for outpatients during the study period. Patients who ordered 5,675 medications（16%）did not have renal function test which was needed. In addition, 2,067 orders（6%）were incorrect dose（over or under）.

Conclusion; The clinical decision support system equipped with recommended antibiotics dose by renal function were useful for outpatients to reduce the inappropriate dose.

Key words：decision support system, renal function, antibiotics, antimicrobial stewardship

背　　景

現在の医療において医療安全は最優先の重要な分野である[1)]。また、指示を行う医師、指示を受ける看護師などは人間であり、エラーは避けられない[2)]。薬剤の中には腎機能等によって調整するべき薬剤がある。しかし、用量調整の必要な全ての薬剤について忙しい臨床医が把握した上で、もれなく調整を行うことは難しい。用量調整がうまくいかなければ過剰投与や過少投与となり副作用発現や治療不全をきたしうることが危惧される。さらに抗微生物薬適正使用の面からも適切な抗微生物薬処方が重要である[3)]。

島根県立中央病院は島根県東部に位置する臨床研修病院である。統合情報システム（IIMS: Integrated Intelligent Management System）を開発し、1999年より稼働している[4)]。IIMS内には、現在入院患者を対象とした抗微生物薬処方時における用量調整を行う臨床決断支援システムが2011年12月より組み込まれ、運用されている。今回は外来患者における同様のシステムの有用性を検討する。2018年９月現在ではツールは画面上に現れていない状態であり、どの程度の影響をもって稼働し、支援しうるかを検証するために、ツールの実行前のデータを検討した。

方　　法

＜概　要＞

入院患者に対する既存のシステムは腎機能を自動計算し、それによる推奨投与量を画面上で医師に示し、医師は最終的に用量を選択することができ、医学的理由から推奨された用量以外の用量を選択することもできるものである。抗微生物薬に関連するものとしては、医師が使用する抗微生物薬を選択した時点で腎機能による推奨の投与量を画面上に表示し、医師が画面から選択できるものである（図１）。これを応用し腎機能に基づいた投薬指示の臨床決断支援システムを外来患者用に開発した。Crや身長が測定されていな

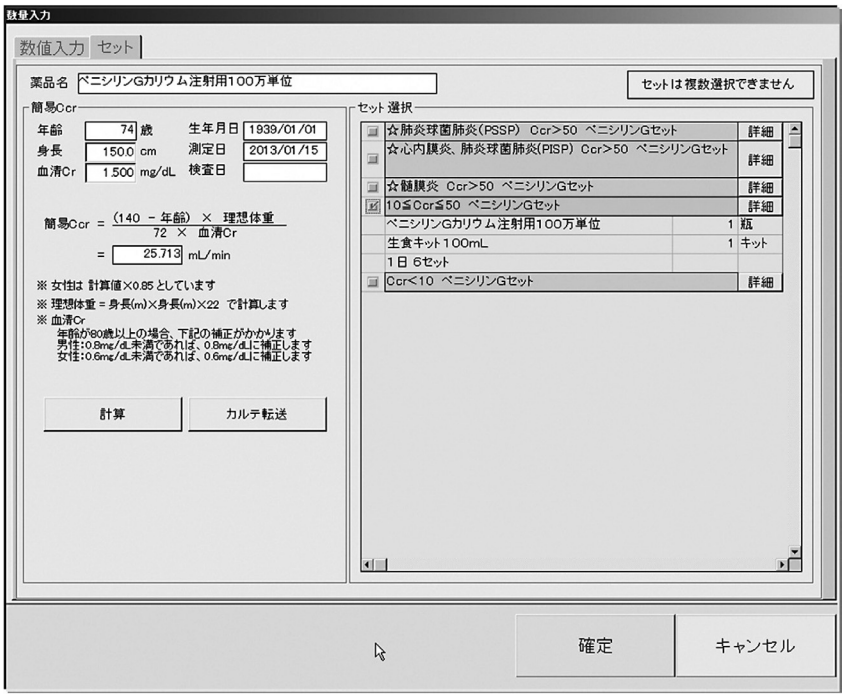

図1　現在の処方画面（入院患者用）
入院患者の注射指示の画面の例である。薬剤「ペニシリンGカリウム」を選択した後に図に示す画面が現れる。年齢、身長、血清クレアチニン値を自動取得し、簡易クレアチニンクリアランスを自動計算する。その簡易クレアチニンクリアランスをもとに推奨する用量のセットを色の変化で示す。病態などで他の処方を選択することも可能である。最終的に指示する処方セットをチェックしてオーダーを発行する。身長などが測定されていない場合は空欄となり自動計算は行わない。その場合は空欄に直接に値を打ち込んで「計算」ボタンを押してオーダーを発行する事も可能である。

ければメッセージが表示される機能を追加することとした。2017年10月よりシステムは稼働しているが、2018年９月時点では実際に画面には出さずバックグラウンドで稼働中である

＜対　象＞

2017年10月から2018年７月までの10か月間。島根県立中央病院で処方された全外来処方のうち、腎機能で調整が必要な処方を行ったものを対象とした。

<推奨投与量＞

推奨投与量は、腎機能で調整が必要な薬剤に対して島根県立中央病院薬剤局が中心となって、主にクレアチニンクリアランスに基づいた腎機能による推奨投与量を定めている（付表）。そのうち抗微生物薬に関しては島根県立中央病院の抗菌薬適正使用支援チーム（AST: Antimicrobial Stewardship Team）および感染制御チーム（ICT: Infection Control Team）が、PK/PD理論をもとに定めた投与量を推奨投与量とした。推奨投与量範囲内（Correct dose）とは、その推奨投与量の範囲内にあるものであり、推奨投与量範囲外（Incorrect dose）とは、推奨投与量範囲内にないもので、過量投与・過少投与と考えられる処方である。

＜データ抽出＞

病院関連の情報は、島根県立中央病院の年報データより抽出した。抽出項目は、2017年のデータで、病床数、職員数、入院患者（総数、性別、年齢）、外来患者（来院部署、来院方法）、外来患者の総処方箋数。

システムに関連するデータの抽出は、島根県立中央病院情報システム管理室において情報処理を専門とする職員が抽出した。抽出項目は、腎機能で調整が必要な処方薬の薬品単位での処方数、抗微生物薬の内容、３か月以内の腎機能測定有無、腎機能が測定されていた場合は推奨投与量範囲内外である。

＜解　析＞

得られたデータをもとに記述統計を行う。数と割合（%）または中央値［四分位値］で表記する。単変量解析において、カテゴリー変数はカイ二乗検定を行った。統計解析は、Stata15を用いて行った。

付表：推奨投与を行う腎機能により調整が必要な薬剤のリスト（主成分のみ）

アテノロール	セフカペン　ピボキシル
アマンタジン	セフジトレン　ピボキシル
アモキシシリン	セフジニル
アログリプチン	セフタジジム
アロプリノール	セフメタゾール
アンピシリン	タゾバクタム・ピペラシリン
アンピシリン・スルバクタム	ダビガトラン
イミペネム・シラスタチン	チアプリド
エナラプリル	テノホビル
エノキサパリン	トラネキサム酸
エプレレノン	ドリペネム
エムトリシタビン・テノホビル	ピオグリタゾン
エリスロマイシン	ピペラシリン
オセルタミビル	ピルシカイニド
オロパタジン	ファモチジン
クラリスロマイシン	フェキソフェナジン
グリクラジド	フェソテロジン
グリベンクラミド	ブシラミン
グリメピリド	フルコナゾール
ソリフェナシン	フレカイニド
ジゴキシン	フロモキセフ
ジソピラミド	ベザフィブラート
シタグリプチン	ベンジルペニシリン
シタフロキサシン	ベンラファキシン
シプロフロキサシン	ホスホマイシン
シベンゾリン	ミノドロン酸
シロドシン	メチルジゴキシン
スルタミシリン	メトホルミン
スルファメトキサゾール・トリメトプリム	メトロニダゾール
	メロペネム
セチリジン	ラコサミド
セファゾリン	ラニチジン
セファレキシン	リセドロン酸
セフェピム	リバーロキサバン
セフォタキシム	レボセチリジン
セフォチアム	ロスバスタチン

＜倫理・COI＞

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結　　果

＜病院統計＞

2017年の島根県立中央病院の病床数は634床、医師数は167名で全職員1,180名のうち14%であった（表

表１　Hospital characteristics（2017）

Shimane Prefectural Central Hospital from 1940 Tertiary educational medical hospital, Japan 1999- Integrated intelligent management system	
Contents	no（%）
Number of beds	634
Medical staff	1,180
Doctors	167（14）
Nurses	687（58）
Paramedical	205（18）
Clerk	121（10）
Patients	
Inpatients	12,340
Age, years, median [IQR]	67 [38-80]
Male	6,197（50）
In hospital death	511（4）
Outpatients	249,733
Emergency Room	21,838（9）
Ambulance	4,068（19）
Doctor helicopter	490（2）
Walking	227,895（91）
Prescription	
Inpatients prescription count	97,466
June, 2017	8,051
Outpatient prescription count	108,223
June, 2017	9,088

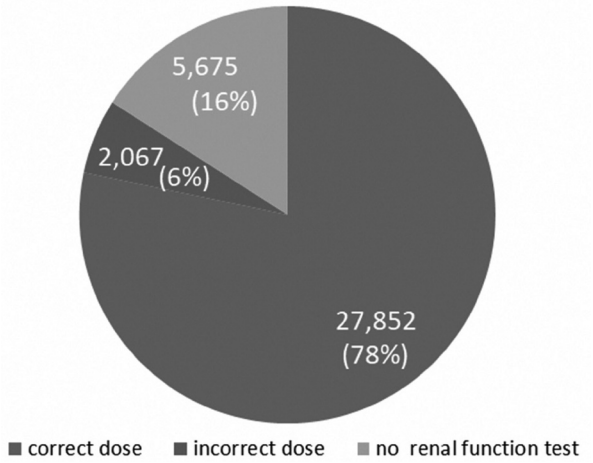

図２　外来処方内容（2017年10月から2018年７月）
10か月間で腎機能での調整が必要な抗微生物薬等の処方は合計35,594処方であった。そのうち5,675（16%）は腎機能が測定されていなかった。腎機能が測定された処方の内、27,852（78%）は腎機能での推奨投与量範囲内であった。2,067（６%）は推奨投与量範囲外であった。

表２　Drugs regulated by renal function

Total drugs	All antibiotics	Oral antibiotics
29,919	7,766（26）	6,495（22）

１）。入院患者数は12,340人で、年齢の中央値は67歳（四分位範囲38-80歳、最小０歳-最大107歳）、男性は6,197人（50%）、院内死亡は511人（４%）であった。外来患者数は249,733名で、救急受診は21,838人（９%）であった。救急受診の内、救急車での来院は4,068名（19%）、ドクターヘリ利用は490名（２%）であった。総処方数は入院で97,466件、外来で108,223件、６月の１か月当たりではそれぞれ8,051件、9,088件であった。

＜処方薬＞

研究期間中における腎機能で調整が必要な薬品数は、薬品単位で35,594件であった（図２）。腎機能が測定されていなかったものは、5,675件（16%）であった。腎機能が測定されていた処方は29,919件（84%）で、腎機能から計算された適切な処方は27,852件（78%）で、適切でないと判断された処方は、2,067件（６%）だった。

腎機能が測定された処方29,919件のうち、抗微生物薬は7,766件（26%）、そのうち経口抗微生物薬は6,495件（22%）であった（表２）。抗微生物薬の推奨投与量範囲内の処方は7,064件（91%）で、推奨投与量範囲外は702件（９%）であった（表３）。抗微生物薬以外の腎機能で調整が必要な薬品の推奨投与量範囲内の処方は20,788件（94%）で、推奨投与量範囲外は1,365件（６%）であった。抗微生物薬処方の方が推奨投与量範囲外の割合が高かった（$p<0.001$）。

経口の抗微生物薬の中では第３世代セフェム系薬の推奨投与量範囲外の割合が36%と高かった（表４）。次いでキノロン剤が８%であった。第３世代セフェムと同系統のβラクタム系でも第１世代セフェムおよび同ペニシリン系は推奨投与量範囲外の割合は３%と第３世代セフェムの十分の一以下であった。マクロライド・ST合剤・その他の抗微生物薬は１-３%であった。抗微生物薬の種別による推奨投与量範囲外の割合には差が認められた（$p<0.001$）。

考　　察

今回我々は腎機能で調整が必要な薬品に対するシステムのベースラインでの稼働状況を解析することによ

表３　Univariate analysis Antibiotics and other drugs regulated by renal function

Classification	All drug	Correct dose	Incorrect dose	*p*-value
Antibiotics	7,766	7,064（91）	702（9）	<0.001
Other	22,153	20,788（94）	1,365（6）	

表４　Breakdown of oral antibiotics

Classification	All antibiotics	Correct dose	Incorrect dose
β-lactam			
Penicillin	1,839	1,787（97）	52（3）
1st Cephem	502	489（97）	13（3）
3rd Cephem	1,509	969（64）	540（36）
Macrolide	1,362	1,346（99）	16（1）
ST	757	734（97）	23（3）
Quinolon	244	224（92）	20（8）
Other	187	183（98）	4（2）
Total	6,495	5,818（90）	677（10）

$p<0.001$

り、システムの有用性について検討した。

病院の特性に関しては、同様の規模の全国の平均とほぼ差がないと考えられた[5]。すなわち、全国の500床以上の平均ベッド数は618、2017年６月の１か月平均入院処方数は8,434、2017年６月の１か月平均外来処方数は11,236、平均医師数は194、医師一人当たりの１か月平均入院処方数は43.5、医師一人当たりの１か月平均外来処方数は57.9との報告に対し、島根県立中央病院ではそれぞれ634、8,051、9,088、167、49.1、55.4であり、同等と考えられる。したがって今回のデータは全国の病院でも応用できる可能性がある。

腎機能で調整が必要な薬品のうち約1/4が抗微生物薬であった。また、抗微生物薬は他の腎機能で調整が必要な薬品よりも推奨投与量範囲外が多かった。過去の研究でもガイドラインで推奨されたアミノグリコシド系抗菌薬投与量の研究[6]、ICUでの腎機能に応じた抗微生物薬量の検討[7]、などにおいても過量投与の調整が必要とされており、抗微生物薬は緊急に処方されることも多いので慎重な処方が検討される。

内服抗微生物薬では第３世代セフェム系薬およびキノロン剤で推奨投与量範囲外が多かった。先行研究では数種類の抗微生物薬での腎機能による決断支援システムはあるが[8]、今回の研究のように65種類以上の薬剤を対応するシステムではないので処方内容の比較は困難ではある。ただ、第３世代セフェム系薬およびキノロン剤は、薬剤耐性（AMR）対策アクションプランでも減量が目標として挙げられており[9]、薬剤の選択の問題のみならず用量でも問題がある傾向にあると考えられた。第３世代セフェム系薬に関しては、他のβラクタム系のペニシリン系・第１世代セフェムが推奨投与量範囲内が多いことを比べて考えると、第３世代セフェム系薬は十分に吟味されずに使用されている可能性がある。今後は用量のみならず、より適切に薬剤の選択ができる方法が望まれる。

今回の研究ではいくつかの限界が挙げられる。１つ目は、単一での施設での状況であること。ただし、同様の病院と処方数などが大きくずれていないのでおおむね同等の規模の病院では当てはまると考えられる。２つ目は、腎機能のみで他の問題（肝障害・アレルギーなど）は検討されていないこと。また一般的には腎機能低下時に用量を下げることは検討されるが、肥満などに対しての用量増量に関してはシステムに組み込まれていないので今後の検討が必要である[10]。３つ目は、今回はベースラインでの検討なので実際の効果は不明で、オーバードーズに関する方策などの対策が今後必要となってくる[11]。これは実際に画面上で表示してからの効果で再検討の必要がある。

結　　語

腎機能による抗微生物薬投与量推奨ツールは臨床決

断支援システムとして有用であり、外来患者に対しても安全に投与するツールとなりうる。

謝　　辞

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ORIGINAL RESEARCH ARTICLE

Differences in Adverse Drug Events Among Pediatric Patients With and Without Cancer: Sub-Analysis of a Retrospective Cohort Study

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Abstract

Objectives This study investigated the differences in the incidence and severity of adverse drug events (ADEs) in pediatric patients with and without cancer.

Methods We used data from the Japan Adverse Drug Events Study for pediatrics, a cohort study enrolling pediatric inpatients at two tertiary care teaching hospitals in Japan. ADEs were identified by on-site review of all medical charts, incident reports, and prescription queries by pharmacists. Two independent physicians reviewed all potential ADEs and classified ADEs in terms of severity and class of causative medication. We compared the incidence and characteristics of ADEs between pediatric cancer patients and non-cancer patients.

Results We enrolled 1189 patients during the study period, 27 with cancer and 1162 without cancer. We identified 480 ADEs in 234 patients (20%): 191 ADEs among 21 cancer patients and 289 ADEs among 213 non-cancer patients (7.1 per patient vs. 0.25 per patient, respectively; $p < 0.0001$). The most common medications associated with ADEs in cancer patients were antitumor agents; in contrast, medications associated with fatal or life-threatening ADEs in cancer patients were most often sedatives (25%) and blood products (25%). Medications associated with fatal or life-threatening ADEs among non-cancer patients were most often sedatives (15%). The percentages of fatal or life-threatening ADEs in cancer patients and non-cancer patients were 2.1 and 4.5%, respectively.

Conclusions Pediatric patients with cancer have a higher risk for ADEs. Although the overall severity was similar between patients with and without cancer, the most common classes of causative medication and medications associated with a higher rate of severe ADEs differed. Application of this information may help minimize the impact of ADEs in pediatric patients.

Key Points

Adverse drug events occurred in pediatric patients with cancer 28 times more frequently than in those without cancer.

As expected, the medications most commonly associated with adverse drug events in pediatric patients with cancer were antitumor agents, but fatal or life-threatening events due to such medications were rare (0.7%).

The category of causative medication and severity of adverse drug events differed between pediatric patients with cancer and without cancer.

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1 Introduction

Adverse drug events (ADEs) are injuries due to medication use. ADEs represent a serious problem in healthcare because they are the most frequent cause of injuries due to medical care in hospitals in developed countries [1, 2]. In Japan, the JADE (Japan Adverse Drug Events) study, a multicenter cohort study, was conducted to estimate the epidemiology of ADEs in several settings [3]. In both Japan and in Western countries, ADEs have been associated with substantial increases in morbidity and mortality [1, 3–5]. Patients who need chemotherapy often experience ADEs as the result of antitumor agents [6]. Pediatric inpatients are vulnerable to ADEs because they often cannot describe their symptoms and have small metabolic reserves [7, 8]. In particular, pediatric cancer patients receiving antitumor agents are at high risk for ADEs because of the nature of the patients and drugs involved [9, 10].

To examine the epidemiology of ADEs in pediatric inpatients, we conducted the JADE study for pediatric patients [11]. As a sub-study, we analyzed differences in ADEs between pediatric patients with and without cancer and evaluated the causes, symptoms, and severity of the ADEs.

2 Methods

2.1 Study Design and Patient Population

This study was based on the data from the JADE study for pediatric inpatients, which was a historical cohort study performed in two tertiary care teaching hospitals in Japan. The details of the study have been described elsewhere [11]. Briefly, we included all patients aged ≤15 years admitted to any ward, including the neonatal intensive care unit (NICU) and pediatric intensive care unit (ICU), and patients aged >15 years admitted to any pediatric ward over a 3-month period in 2009. Because some adult patients with congenital or metabolic diseases were cared for by pediatricians from a young age, such patients were included in this cohort study based on the protocol. We excluded neonates in well-baby nurseries from this study because they were healthy and not cared for by pediatricians. If neonates had a problem such as temporary dyspnea or mild cyanosis of the limbs at birth, they were admitted to the NICU and cared for by neonatologists. We included these neonates in this study. We categorized the age groups as follows: neonates (aged <1 month), infants (1 month to <1 year), preschoolers (1 year to <7 years), school-aged children (7 to <13 years), teenagers (13 to <19 years), and adults (≥19 years).

The institutional review boards of the two participating hospitals approved the study. Because all data were obtained as part of routine daily practice, the institutional review boards waived the need for informed consent.

2.2 Definitions

The primary outcome of the study was the occurrence of ADEs, which we compared between pediatric patients with and without cancer. Cancer patients were defined as those who were diagnosed with any malignant tumor or those who had a tumor and were receiving antitumor agents. Non-cancer patients included those with benign or other tumors. We used validated methodology for the classification of ADEs [12]. An ADE was defined as a health injury occurring because of medication use. For example, nausea or vomiting in a patient receiving an antitumor agent was considered an ADE. We categorized the severity of ADEs as follows: fatal (resulting in death), life-threatening (requiring transfer to the ICU or causing anaphylactic shock), serious (neutropenia requiring a special protective environment, cutaneous lesions requiring therapy, gastrointestinal bleeding, altered mental status, excessive sedation, increased creatinine level, or decreased blood pressure), or significant (rash, diarrhea, or nausea). Categories of ADE symptoms included bleeding; central nervous system; allergic or skin reaction; liver or metabolic dysfunction; cardiovascular; gastrointestinal; renal; respiratory; bone marrow suppression or cytopenia; and other.

We categorized medications as follows: antihistamines, antibiotics, antitumor agents, adrenaline/anticholinergics, blood products, hematopoietic drugs, anticoagulants, diuretics/cardiovascular agents, antipyretic analgesics/nonsteroidal anti-inflammatory drugs (NSAIDs), anticonvulsants, sedatives, antipsychotics, diagnostic drugs/electrolytes and fluids/others, antitussives, ophthalmic/otolaryngologic/dermatologic drugs, laxatives, local anesthetics, corticosteroids, hormones/insulin, aminophylline, and peptic ulcer drugs. Antitussives did not include codeine but did include expectorants, and sedatives did not include narcotics or opiates. Because doses for pediatric patients were generally determined by body weight, and the standard doses varied between drugs, we did not account for dose in the analyses.

2.3 Data Collection and Review Process

Trained reviewers based at each participating hospital reviewed all medical charts, laboratory results, incident reports, and prescription queries from pharmacists. The trained reviewers included a board-certified pediatrician,

pediatric nurses, and a dietitian; the pediatrician trained all reviewers in a standard manner, as reported elsewhere [12]. Reviewers collected the characteristics and administrative data for all patients enrolled in the cohort and identified potential ADEs and associated details, such as detailed symptoms and drug name, dose, route, and class.

After data collection, two independent physician reviewers assessed, in a standard manner, whether any potential ADEs should be classified as ADEs [12]. Briefly, the reviewers summarized and discussed many aspects, including preceding drugs, other causative conditions occurring during hospitalization, previous literature reports, alleviation after discontinuation of drug, repeated symptoms when the same drug was re-introduced, and so on. They classified the severity, symptoms, and class of medication involved in ADEs. When disagreement arose over classification of an event, the reviewers reached consensus through discussion. Uncertain symptoms or those for which consensus was not reached were excluded from the ADEs.

2.4 Statistical Analyses

Categorical variables regarding patient characteristics are reported as numbers and percentages. A Chi squared test was used to compare patients with and without cancer. We also constructed a logistic regression model for cancer patients who developed ADEs, adjusting for the age group and admission to an ICU. The likelihood of ADEs was expressed as an odds ratio (OR) and its 95% confidence interval (CI). The ADE rate per 100 patients, ADE severity, and ratio of ADE severity for each drug were compared between cancer and non-cancer patients; the Chi squared test was used for categorical variables.

We carried out all analyses using JMP 12.0 software (SAS Institute Inc., Cary, NC, USA). Two-tailed p values <0.05 were considered statistically significant.

3 Results

3.1 Patient Characteristics

Among the 1189 patients included in the JADE study for pediatrics, 480 ADEs occurred in 234 (20%) patients. Among the different age categories, there were 252 (21%) neonates, 174 (15%) infants, 465 (39%) preschoolers, 189 (16%) school-aged children, 98 (8%) teenagers, and 11 (1%) adults (Table 1). The age of adults ranged from 20 to 42 years.

Antibiotics (61%), antipyretic analgesics/NSAIDs (32%), adrenaline/anticholinergics (26%), and antitussives (26%) were the three most frequent classes of prescribed medication on admission.

3.2 Comparison of Cancer Patients and Non-Cancer Patients

In all, we included 27 cancer patients and 1162 non-cancer patients in this study. One patient with teratoma and another with optic glioma were categorized as cancer patients because they received chemotherapy during the hospitalization. Patients with cancer had more operations and received antitumor agents or anticoagulants more often than those without cancer (Table 1). On the other hand, patients without cancer more often received adrenaline/anticholinergics and antipyretic analgesics/NSAIDs. Overall, 191 ADEs occurred in 21 cancer patients and 289 ADEs occurred in 213 non-cancer patients. The ADE rate per 100 patients in cancer patients was 707 compared with 25 in non-cancer patients ($p < 0.0001$). The adjusted OR of ADEs among patients with cancer was 12.3 (95% CI 4.9–31.1) compared with patients without cancer.

The severity of ADEs in cancer patients was similar to that in non-cancer patients ($p = 0.13$). The percentages of fatal or life-threatening ADEs in cancer patients and non-cancer patients were 2.1 and 4.5%, respectively (Fig. 1).

Among 191 ADEs in cancer patients, 149 (78%) were associated with antitumor agents, 13 (7%) with corticosteroids, ten (5%) with antibiotics, and eight (4%) with sedatives. In contrast, among 289 ADEs in non-cancer patients, 135 (47%) were associated with antibiotics, 52 (18%) with sedatives, 21 (7%) with corticosteroids, and 13 (4%) with antipyretic analgesics/NSAIDs (Fig. 2).

In contrast to all ADEs, medications with a high frequency of fatal or life-threatening ADEs among cancer patients included sedatives (25%) and blood products (25%); those among non-cancer patients included anticoagulants (50%), sedatives (15.4%), and hormones/insulin (50%), although the sample size was small (Fig. 3).

3.3 Adverse Drug Events (ADEs) Due to Antitumor Agents

Among the 27 cancer patients, 149 ADEs occurred in 18 patients due to antitumor agents, for a rate of 552 per 100 patients. Analysis of the severity of ADEs due to antitumor agents showed there was one (0.7%) life-threatening ADE, 43 (29%) serious ADEs, and 105 (70%) significant ADEs. Symptom categories of ADEs due to antitumor agents included five (3%) bleeding, eight (5%) central nervous system, 11 (8%) allergic or skin reaction, 17 (11%) liver or metabolic dysfunction, one (0.7%) cardiovascular, 58 (39%) gastrointestinal, four (3%) renal, one (0.7%)

Table 1 Patient characteristics

Characteristics	All ($n = 1189$)	Cancer patients ($n = 27$)	Non-cancer patients ($n = 1162$)	p value
Age				
Neonate (<1 month)	252 (21)	0 (0)	252 (22)	0.02
Infant (1 month to <1 year)	174 (15)	5 (19)	169 (15)	
Preschooler (1 to <7 years)	465 (39)	12 (44)	453 (39)	
School-aged (7 to <13 years)	189 (16)	4 (15)	185 (16)	
Teenager (13 to <19 years)	98 (8)	6 (22)	92 (8)	
Adult (≥19 years)	11 (1)	0 (0)	11 (1)	
Sex				
Male	649 (55)	18 (67)	631 (54)	0.2
Surgery during hospitalization	294 (25)	14 (52)	280 (24)	0.001
Drug after admission				
Antihistamines	244 (21)	8 (30)	236 (20)	0.24
Antibiotics	727 (61)	19 (70)	708 (61)	0.32
Antitumor agents	4 (0.3)	3 (11)	1[a] (0.1)	<0.0001
Adrenaline/anticholinergics	309 (26)	1 (4)	308 (27)	0.006
Blood products	28 (2)	0 (0)	28 (2)	1.0
Hematopoietic drugs	24 (2)	0 (0)	24 (2)	1.0
Anticoagulants	86 (7)	6 (22)	80 (7)	0.002
Diuretics/cardiovascular agents	119 (10)	2 (7)	117 (10)	1.0
Antipyretic analgesics/NSAIDs	383 (32)	3 (11)	380 (33)	0.02
Anticonvulsants	173 (15)	7 (26)	166 (14)	0.09
Sedatives	69 (6)	4 (15)	65 (6)	0.07
Antipsychotics	13 (1)	0 (0)	13 (1)	1.0
Diagnostic drugs/electrolytes and fluids/others	967 (81)	21 (78)	946 (81)	0.63
Antitussives	305 (26)	3 (11)	302 (26)	0.12
Ophthalmic/otolaryngologics/dermatologics	154 (13)	2 (7)	152 (13)	0.56
Laxatives	191 (16)	6 (22)	185 (16)	0.38
Local anesthetics	39 (3)	2 (7)	37 (3)	0.22
Corticosteroid	138 (12)	6 (22)	132 (11)	0.08
Hormones/insulin	24 (2)	2 (7)	22 (2)	0.1
Aminophylline	67 (6)	0 (0)	67 (6)	0.4
Peptic ulcer drugs	111 (9)	2 (7)	109 (9)	1.0

Data are presented as n (%) unless otherwise indicated

ADEs adverse drug events, *NSAIDs* non-steroidal anti-inflammatory drugs

[a] One patient without cancer received an antitumor agent to treat a non-malignant condition

respiratory, 37 (25%) bone marrow suppression or cytopenia, and seven (5%) other.

4 Discussion

The rate of ADEs in pediatric patients with cancer was higher than in those without cancer—cancer patients had seven ADEs on average. Although the sample size of cancer patients was small, the overall severity of the ADEs seemed similar between cancer and non-cancer patients. While most of the ADEs for cancer patients were caused by antitumor agents, most of the fatal or life-threatening ADEs were caused by sedatives and blood products. The classes of drugs causing fatal or life-threatening ADEs seemed to differ between pediatric patients with cancer and those without.

Data on ADEs among pediatric patients with cancer are sparse. For example, Takata et al. [13] found that pediatric patients with cancer more frequently experienced ADEs and that hematology and oncology wards had a higher incidence of ADEs. In this study, while we found that

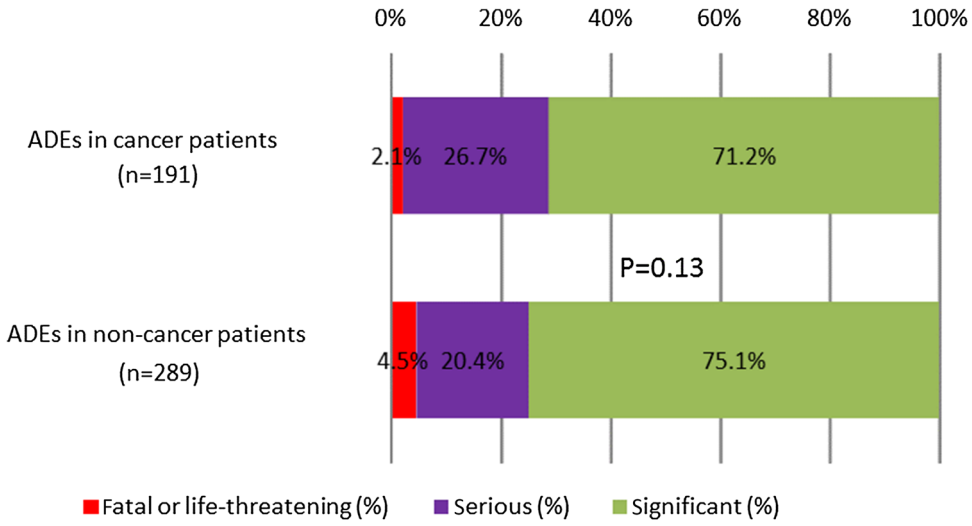

Fig. 1 Comparison of adverse drug event severity between cancer patients and non-cancer patients. *ADEs* adverse drug events

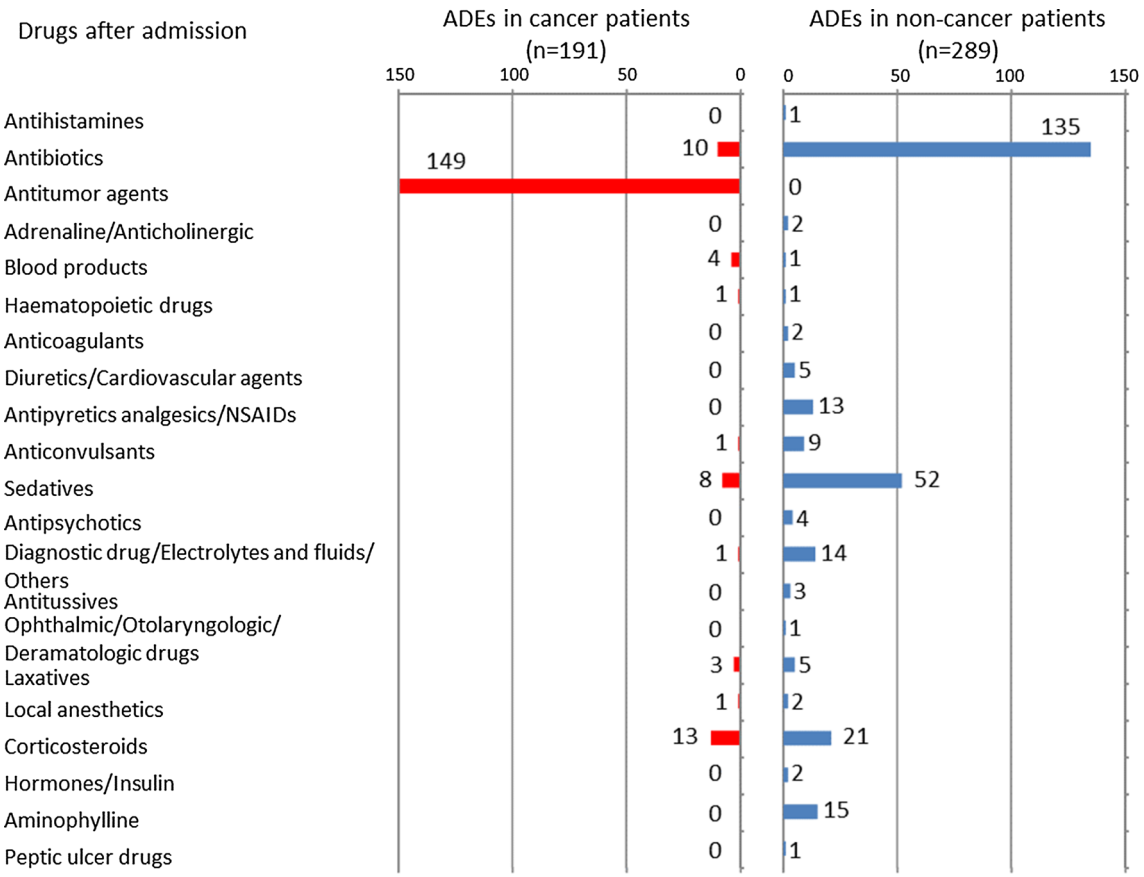

Fig. 2 Causative drugs of adverse drug events. *ADEs* adverse drug events, *NSAIDs* non-steroidal anti-inflammatory drugs

ADEs occurred frequently in pediatric cancer patients, the rate of fatal or life-threatening ADEs was much lower (2.1%). A systematic review of studies in pediatric patients with leukemia reported treatment-related mortality (which should be considered an ADE) of 3.6% [14], which is similar to the rate in our data. The higher incidence of all ADEs but comparable risk for fatality in the current study might be because we proactively collected all ADEs in a standard manner, and most ADEs were minor injuries.

The prevalence of ADEs by medication classes differs between settings. For example, one study in hospitalized adults found that 32% of ADEs due to antitumor agents were fatal [15]. Moreover, another study [16] in patients with unplanned cancer admissions found that 13% had

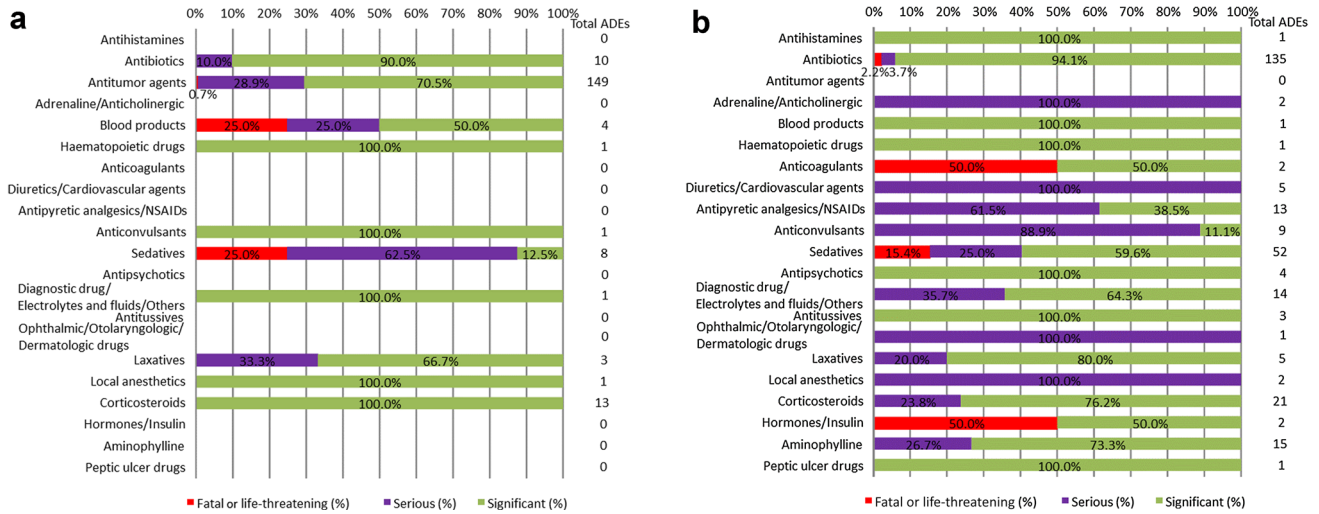

Fig. 3 Severity of adverse drug events in **a** cancer and **b** non-cancer patients. *ADEs* adverse drug events, *NSAIDs* non-steroidal anti-inflammatory drugs

ADEs. Furthermore, Nazer et al. [15] reported that, among oncology patients, the medications most commonly associated with an ADE requiring ICU admission were antitumor agents, analgesics, and anticoagulants. In contrast, in the current study in the pediatric setting, only one (0.7%) fatal or life-threatening ADE due to antitumor agents occurred, although the number of patients evaluated was small.

As sepsis from febrile neutropenia (FN) sometimes causes a fatal ADE, it is an important type of ADE due to antitumor agents. Admittance for FN has been reported to be 4.4 per 100 oncology admissions [16], with an annual incidence of 19.4 cases of FN per 1000 oncology admissions [17]. Because we classified such symptoms as bone marrow suppression rather than FN, the incidence of bone marrow suppression was higher, at 205 per 100 cancer patients. This provides additional evidence that antitumor agents as a class are most commonly associated with ADEs.

We must recognize that drugs with great benefit generally have a high rate of ADEs. Moreover, differences were apparent between the drug classes causing ADEs in cancer patients compared with in non-cancer patients. Such differences should be noted to assist with awareness and proper monitoring when these drugs are administered. Although the frequency of ADEs due to antitumor agents was high, the high risk for fatal or life-threatening ADEs with other drugs, namely blood products and sedatives, should also be considered for pediatric patients with cancer.

Our study has several limitations. First, the number of pediatric patients with cancer was much smaller than that without cancer, so we could not draw definitive conclusions. On the other hand, this study was conducted at a daily clinical setting, and the findings reflect real-world data. Second, we conducted this pediatric study at two tertiary care teaching hospitals. Therefore, the results are not generalizable to non-tertiary care teaching hospitals, in which most children receive medical care in Japan. Third, some ADEs may not have been noted in the charts and may thus not have been detected, potentially resulting in underestimation of ADEs. In addition, because many ADEs due to antitumor agents are well-known and noticeable, other ADEs in cancer patients might have been overlooked. However, more robust alternatives to measure ADEs have not yet been developed. Finally, the classification of ADEs seemed arbitrary, and many symptoms were difficult to classify as ADEs or other conditions. However, we determined the most likely causative drug based on the historical evidence from the literature, and this method is the best one currently available.

5 Conclusion

Pediatric patients with cancer had more frequent ADEs than did those without cancer. While most ADEs in cancer patients were caused by antitumor agents, other medications caused the greatest proportion of fatal or life-threatening ADEs. The overall severity of ADEs in patients with and without cancer was similar. Nonetheless, knowing which medication classes have higher risks for ADEs in pediatric patients with and without cancer may help providers more carefully use those medications and monitor patients, which may in turn help to minimize the impact of ADEs in pediatric patients overall.

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Compliance with Ethical Standards

Informed consent The institutional review boards of the two participating hospitals approved the study. Because all data were obtained as part of routine daily practice, the institutional review boards waived the need for informed consent.

Conflict of interest Drs. Koizumi, Ohta, Sakuma, Okamoto, Matsumoto, and Morimoto have no conflicts of interest. Dr. Bates received equity from Intensix, which makes software to support clinical decision making in intensive care; is named as co-inventor on patent no. 6029138 held by Brigham and Women's Hospital (Boston, MA, USA) on the use of decision-support software for medical management licensed to the Medicalis Corporation; holds a minority equity position in Medicalis, which develops web-based decision support for radiology test ordering; consults for EarlySense, which makes patient safety monitoring systems; has received equity and cash compensation from QPID Inc., a company focused on intelligence systems for electronic health records; has received cash compensation from CDI (Negev) Ltd., a not-for-profit incubator for health IT startups; and has received equity from Enelgy, which makes software to support evidence-based clinical decisions, from Ethosmart, which makes software to help patients with chronic diseases, and from MDClone, which takes clinical data and produces de-identified versions of it.

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Ethical approval This study was approved by all institutional review boards at all participating hospitals and was conducted in accordance with the provisions of the Declaration of Helsinki and the ethical guidelines for clinical studies in Japan.

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RESEARCH ARTICLE Open Access

The epidemiology of adverse drug events and medication errors among psychiatric inpatients in Japan: the JADE study

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Abstract

Background: Knowledge of the epidemiology of adverse drug events (ADEs) and medication errors in psychiatric inpatients is limited outside Western countries. The nature of ADEs and medication errors are important for improving the quality of care worldwide; therefore, we conducted the Japan Adverse Drug Events Study, a series of cohort studies at several settings in Japan.

Methods: This report included 448 inpatients with 22,733 patient-days in a psychiatric hospital and psychiatric units at a tertiary care teaching hospital over 1 year. Four psychiatrists and two other physicians reviewed all medical charts and related documents to identify suspected incidents. The physicians later classified those incidents into ADEs, potential ADEs, medication errors, or exclusions and evaluated the severity and preventability if the incidents were events.

Results: During the study period, we identified 955 ADEs and 398 medication errors (incidence: 42.0 and 17.5 per 1000 patient-days, respectively). Among ADEs, 1.4 %, 28 %, and 71 % were life-threatening, serious, and significant, respectively. Antipsychotics were associated with half of all ADEs. The incidence of medication errors was higher in medical care units than in acute and nursing care units (40.9, 15.6, and 17.4 per 1000 patient-days, respectively). The monitoring and ordering stages were the most common error stages (39 % and 34 % of all medication errors, respectively), and 76 % of medication errors with ADEs were found at the monitoring stage. Non-psychiatric drugs were three times as likely to cause ADEs with errors compared to psychiatric drugs.

Conclusions: Antipsychotic use, inadequate monitoring, and treatment of physical ailments by psychiatrists may contribute to the high incidence of medication errors and ADEs among psychiatric inpatients in Japan. Psychiatrists should be cautious in prescribing antipsychotics or unfamiliar medications for physical problems in their psychiatric patients, and should monitor patients after medication administration.

Keywords: Adverse drug event, Medication error, Epidemiology, Psychiatry, Patient safety

Abbreviations: ADE, Adverse drug event; CI, Confidence interval; IQR, Interquartile range; SD, Standard deviation

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Background

Adverse drug events (ADEs) are drug-related injuries resulting from medical intervention [1–3]. ADEs are generally the most frequent cause of injuries due to medical care in hospitals [4, 5]. Psychiatric inpatients are at high-risk for these injuries because pharmacotherapy plays a central role in psychiatric treatment [6, 7]. In addition, many psychiatric patients present with comorbid medical disorders that require treatment with non-psychiatric drugs, and when these conditions are treated in psychiatric hospitals, this puts patients at further risk for ADEs and medication errors [7, 8].

There is a need for more epidemiological data concerning appropriate medication use in order to provide safer and more effective pharmacological treatment for psychiatric inpatients. Previous studies, however, have noted the complexities of identifying ADEs and medication errors in psychiatric settings because it is difficult to distinguish ADEs caused by drugs from symptoms related to mental disorders; in addition, it can be difficult to define medication errors in these settings, as psychiatric pharmacotherapy often deviates from standard treatment [9, 10]. In fact, there have been notably few comprehensive studies on this topic, especially regarding ADEs [7, 11–13]. Furthermore, the studies that have been conducted all took place in Western countries, meaning that their results cannot be generalized to clinical settings in other countries without first assessing local data [14], because mental health services differ between countries. For example, longer hospital stays and lower staff ratios are two characteristics of Japanese psychiatric care [15], while many African countries suffer from a critical lack of psychiatrists and pharmacists [16]. To this end, we conducted a historical cohort study in psychiatric settings to estimate the incidence and nature of ADEs and medication errors among psychiatric inpatients in Japan.

Methods

Study design and patient population

This historical cohort study was conducted as part of a multicenter cohort study known as the Japan Adverse Drug Events (JADE) Study [17, 18]. As part of the JADE study series, we collected information using the standard JADE protocol. [3, 17, 18] Data were collected from the psychiatric inpatient units at one psychiatric hospital and one tertiary care teaching hospital. There were a total of 438 psychiatric inpatient beds between these two hospitals, including beds in acute care units, nursing care units, and medical care units. The acute care unit comprises the main section of a psychiatric department in which patients with an acute mental disorder receive targeted mental care. Psychiatric patients who have recovered from the acute stage of their condition but who still require nursing care are admitted to nursing care units. Medical care units are specialized sections within a psychiatric department that provide treatment to psychiatric patients with physical medical conditions. Both hospitals included in this study used electronic medical records.

At the tertiary care teaching hospital, patients were treated both by attending psychiatrists and by resident psychiatrists, who have <3 years of training after obtaining their medical license. Resident psychiatrists practiced under the supervision of attending psychiatrists and primarily ordered medications. In contrast, most of the psychiatrists at the psychiatric hospital were attending psychiatrists. Both hospitals admitted patients to the acute care or medical care units within the psychiatry department if psychiatric disorders were the main presenting problem and the patients' physical problems were considered to be mild; internists provided medical consultations as needed. Conversely, if patients' physical complications were considered to be more severe than their psychiatric problems, or if patients required intensive care (for example, as a result of myocardial infarction or femoral fracture, or if they required intubation), they were discharged from the psychiatric department and transferred to non-psychiatric wards for subsequent care.

Data were collected from all psychiatric inpatients who were admitted to and discharged from the acute, nursing and medical care units from April 1, 2010 through March 31, 2011. The main measures that were evaluated were patient-days and the number of admissions. The study was approved by the institutional review boards of the Kyoto Prefectural University of Medicine and by the institutional review boards of the two participating hospitals. The need for informed consent was waived because all data were collected as part of the hospitals' daily practices.

Definitions

The primary outcome measured in this study was the number of ADEs, defined as drug-related injuries resulting from medical intervention [1, 2]. The term ADE has a wide spectrum of definitions, including harm caused by drugs at a usual dosage (adverse drug reactions: ADRs) or at an unusual dosage, and also including harm from dose reduction and discontinuation of drug therapy [19]. For example, an extrapyramidal symptom, such as akathisia, occurring after a patient receives antipsychotics, and with no other apparent cause, is considered to be an ADE. Rebound insomnia that occurs following discontinuation of sedatives is another example of an ADE. An ADE was then categorized by severity as fatal, life-threatening, serious or significant. Fatal ADEs were those that resulted in death. Life-threatening ADEs were those that caused such issues as respiratory depression or suicidal behavior. Serious ADEs included gastrointestinal bleeding, falls, or a

decrease in blood pressure. Significant ADEs included cases with milder symptoms, such as diarrhea, constipation, extrapyramidal symptoms or drowsiness.

A secondary outcome that was measured in this study was medication errors. Medication errors could occur at any step of the medication use process (ordering, transcribing, dispensing, administering or monitoring), and medication errors may or may not cause ADEs. If a medication error was found, the type of error and the stage in the process where it occurred were classified. The medication use process included the following stages: ordering by psychiatrists or other physicians; transcription by nurses; dispensing by pharmacists (or by psychiatrists and nurses, as was the case during the night shift and on weekends in the psychiatric hospital); administration by nurses or by patients; and monitoring by psychiatrists, other health professionals or by patients themselves.

ADEs were categorized as either preventable or non-preventable. An ADE was considered to be preventable if it resulted from a medication error or was otherwise ameliorable by available means (e.g., switching to a different drug or cautious monitoring after administration). An ADE that occurred in the absence of a medication error was defined as a non-preventable ADE. For example, a rash that occurred due to lamotrigine use in a patient without a history of lamotrigine-induced rash would not be considered a preventable ADE, but it would be considered as a preventable ADE if the patient had a history of such a rash.

We also classified ADEs according to their potential for causing injury. A potential ADE was an error that had the potential for injury but did not actually result in injury, either because of specific circumstances, chance, or because the error was intercepted. For example, if hypnotics were administered several hours earlier than prescribed, this would constitute a medication error and potential ADE, even if no negative effects were observed because hypnotics may cause immediate somnolence. On the other hand, early administration of anti-dementia drugs would be classified as a medication error but not a potential ADE because the drug rarely causes acute side effects.

Data collection and classification

The definitions and methods used in this study were consistent with those from prior studies on this topic [3, 17, 18]. In this study, four psychiatrists and two physicians, all with experience in the classification of ADEs as a result of previous research on this topic, reviewed all patient charts from each participating hospital, along with laboratory results, incident reports and prescription queries. Research assistants used patient charts to compile demographic characteristics and administrative data for all enrolled patients in the cohort.

Once all data were collected from participating hospitals, the reviewers independently classified relevant incidents as an ADE, potential ADE or medication error, while also recording the details of those incidents. This included information about the name, dose, route and class of the drugs, the details of symptoms resulting from ADEs, and the details related to medication errors such as type, stage and persons who were in charge at the time the error occurred. The reviewers also independently classified all incidents according to their severity and preventability. After all suspected incidents were collected, the reviewers met to confirm the final classification for each incident. When the reviewers disagreed on the classification of an incident, they reached a consensus through discussion.

Statistical analyses

The incidences per 1000 patient-days, crude rates per 100 admissions, and 95 % confidence intervals (CIs) were calculated as a whole and by unit types (acute care unit, nursing care unit, and medical care unit). Continuous variables are presented as means with standard deviations (SDs) or medians with interquartile ranges (IQRs), and categorical variables are shown as numbers and percentages. We used the χ^2 test to assess the relationship between drug classes and preventable ADEs. We calculated inter-rater reliabilities using k statistics. Kappa scores between reviewers regarding the presence of an ADE were 0.96 (ADE v. potential ADE or exclude). The kappa for preventability was 0.95 (preventable v. non-preventable), while the kappa for severity was 0.43 (significant v. serious or life-threatening). These values were similar to those published in previous reports by Rothschild et al. (2007) and Morimoto et al. (2011). We performed all analyses using JMP V.11.2 (SAS Institute, Cary, North Carolina, USA) software.

Results

There were a total of 448 admissions with 22,733 patient-days during the study period. The ages of the included patients ranged from 13 to 97 years old, and the mean age was 56 (SD 22) years. Forty-one (185/448) percent of patients were aged ≥65 years, and 247 (55 %) were female. The median hospital stay was 32 (interquartile range 15–75) days. The acute care, nursing care and medical care units admitted 341 (76 %), 75 (17 %), and 32 (7 %) patients, respectively (Table 1). Of all admissions, approximately 42 % were involuntary admissions. The most common reasons for admission were schizophrenic disorders and dementia, and the median number of medications patients were taking on admission was 6 (range 4–8) (Table 1).

Adverse drug events

We identified 1234 suspected incidents, and through reviews and discussions of these suspected incidents, we identified 955 ADEs among 283 patients (63 %) (Fig. 1). The incidence of ADEs was 42.0 [95 % CI 39.4–44.6] per

Table 1 Demographic data for the study population

Factors	No. of patients
	Total (*n* = *448*)
Age ≥ 65 years, *n* (%)	185 (41)
Female, *n* (%)	247 (55)
Admitting unit, *n* (%)	
Acute	341 (76)
Nursing	75 (17)
Medical	32 (7)
Admission pathway, *n* (%)	
Scheduled admission	247 (55)
Emergency admission	201 (45)
Nonresident physician in charge, *n* (%)	379 (85)
Involuntary admission, *n* (%)	186 (41.5)
Number of prescribed medications on admission, median (quartile)	6 (4–8)
Primary diagnosis,[a] *n* (%)	
Dementia	97 (21.7)
Other organic disorders	19 (4.2)
Mental or behavioral disorder due to substance use	48 (10.7)
Schizophrenia and other psychotic disorders	113 (25.2)
Mood disorders	84 (18.8)
Depression	38 (8.5)
Mania, Bipolar disorder	32 (7.1)
Other mood disorders	14 (3.1)
Neurotic, stress-related and somatoform disorders	40 (8.9)
Anorexia	17 (3.8)
Mental retardation	11 (2.5)
Development disorder	12 (2.7)
Other	7 (1.6)

[a]Diagnoses based on the International Classification of Diseases, Tenth Revision [24]

1000 patient-days, and the crude rate was 213 [95 % CI 184–243] per 100 admissions (Table 2). Significant ADEs accounted for 71 % (677 events in 263 patients) of all events, followed by serious ADEs (28 %, 265 in 124) and life-threatening ADEs (1.4 %, 13 in 12). There were no fatal ADEs that occurred during the study.

The most common class of drugs associated with ADEs was atypical antipsychotics (34 %, 323/955), and almost half of ADEs (46.9 %, 448/955) were associated with typical and atypical antipsychotics. Non-psychiatric drugs accounted for 16 % (124/789) of non-preventable ADEs, but were associated with 42 % (69/166) of all preventable ADEs. In other words, the proportion of preventable ADEs to all ADEs associated with non-psychiatric drugs (69 per 193 ADEs; 36 %) was higher compared to psychiatric drugs (97 per 762 ADEs; 13 %) ($P < 0.001$) (Table 3).

When ADEs were assessed by organ system, central nervous system symptoms (including falls, over-sedation and extrapyramidal symptoms) were the most frequent symptoms, accounting for 44 % (415/995) of all ADEs, followed by gastrointestinal symptoms (including diarrhea and constipation) (34 %, 326/955), allergic or skin symptoms (including drip leakage) (6 %, 58/955) and metabolic or liver dysfunction (5 %, 49/955).

Medication errors and potential adverse drug events

We identified 398 medication errors among 174 patients (39 %). The incidence was 17.5 [95 % CI 15.8–19.2] per 1000 patient-days, and the crude rate was 88.8 [95 % CI 72.9–105] per 100 admissions. Among the 398 medication errors, 166 actually resulted in ADEs and were therefore classified as preventable ADEs, whereas 186 had the potential to cause injury but did not result in observed harm (Fig. 1). The incidence and crude rates were approximately two times higher in the medical care units compared to the other units. Furthermore, the

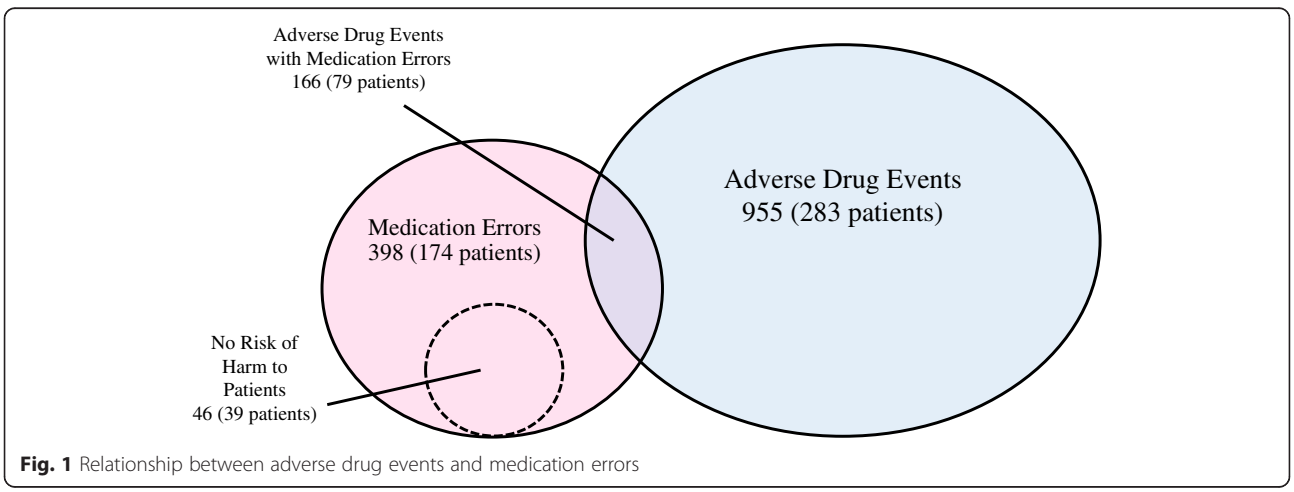

Fig. 1 Relationship between adverse drug events and medication errors

Table 2 Incidences of adverse drug events, medication errors and preventable adverse drug events

Unit	*n*	Patient-days	ADEs	Incidence[a]	95 % CI	Crude rate[b]	95 % CI
Acute	341	16834	725	43.1	40.0–46.1	213	179–246
Nursing	75	4480	157	35.0	29.7–40.4	209	144–275
Medical	32	1419	73	51.4	40.0–62.9	228	88.6–368
Total	448	22733	955	42.0	39.4–44.6	213	184–243
Unit	*n*	Patient-days	Medication Errors	Incidence[a]	95 % CI	Crude rate[b]	95 % CI
Acute	341	16834	262	15.6	13.7–17.4	76.8	62.0–91.7
Nursing	75	4480	78	17.4	13.6–21.2	104	56.3–152
Medical	32	1419	58	40.9	30.6–51.2	181	73.4–289
Total	448	22733	398	17.5	15.8–19.2	88.8	72.9–105
Unit	*n*	Patient-days	Preventable ADEs	Incidence[a]	95 % CI	Crude rate[b]	95 % CI
Acute	341	16834	86	5.1	4.0–6.2	25.2	16.4–34.1
Nursing	75	4480	38	8.5	5.8–11.2	50.7	17.5–83.8
Medical	32	1419	42	29.6	20.8–38.4	131	35.9–227
Total	448	22733	166	7.3	6.2–8.4	37.1	25.8–48.3

ADEs adverse drug events, *CI* confidence interval
[a]Per 1000 patient-days
[b]Per 100 admissions

incidence of preventable ADEs in the medical care units (29.6) was much higher compared to the acute care units (5.1) and nursing care units (8.5) (Table 2).

The incidence of preventable ADEs and non-preventable ADEs was 7.3 [95 % CI 6.2–8.4] and 34.7 [95 % CI 32.3–37.1] per 1000 patient-days, respectively. Thus, 17.4 % (166/955) of ADEs were considered preventable. The incidence of potential ADEs was 8.2 [95 % CI 7.0–9.4] per 1000 patient-days. Forty-six medication errors were determined to carry no risk of injury to patients, so these errors were not considered to be potential ADEs. Twelve percent of potential ADEs (23 cases) were intercepted before a drug was administered and were thus classified as intercepted potential ADEs. Medication errors were most frequently associated with the monitoring stage (39 %, 155/398) and ordering stage (34 %, 134/398) of treatment. In addition, 76 % (126/166) of preventable ADEs occurred during the monitoring stage. Potential ADEs occurred most frequently during the ordering stage, accounting for 46 % (86/186) of all potential ADEs, followed by the administering stage (36 %, 67/186).

Discussion

We determined that ADEs and medication errors were common in Japanese psychiatric inpatient settings. ADEs were observed in 63 % of psychiatric inpatients with an incidence of 42 per 1000 patient-days, and medication errors were observed in 39 % of inpatients with an incidence of 17.5 per 1000 patient-days. Most of these ADEs were not preventable (83 % of ADEs), and 29 % of ADEs were classified as serious or life-threatening. In addition, we identified frequent medication errors at the monitoring stage (39 % of all medication errors), and this was more evident for preventable ADEs (76 % of all preventable ADEs occurred at this stage).

Comparison with findings from previous studies in psychiatric settings

Although there have been several previous studies on ADEs (or ADRs) and medication errors in psychiatric settings, comparisons between the previous studies were difficult because they used different designs and denominators [20]. In addition, among studies utilizing the same denominator but with different study designs, there were significant differences in the reported rates of medication errors (e.g., 0.79 potential ADEs per 1000 patient-days based on a reporting system [21] vs. 1516 medication errors per 1000 patient-days on a retrospective chart review [8]). Therefore, in order to compare our findings with those of previous studies in different settings, we adopted the same definition and methodology used in the study performed by Rothschild et al., which took place in psychiatric settings in the USA [7], as well as those of other studies in general settings in the USA [2] and Japan [17]. In comparison with the present study, Rothschild et al. reported one-quarter incidence of ADEs (10 per 1000 patient-days) and one-third medication errors (6.3 per 1000 patient-days). The difference become even more evident regarding the crude rate of ADEs per 100 admissions (213 v. 10.2) and medication errors (88.8 v. 6.4); this is likely a result of the fact that the mean length of stay is much longer in Japan compared to the USA (50.7 v. 10.3 days).

Table 3 Frequency of adverse drug events according to drug class

Drug Class	ADEs, *n* (%) (*n = 955*)	Preventable ADEs, *n* (%) (*n = 166*)	Non-preventable ADEs, *n* (%) (*n = 789*)	Potential ADEs, *n* (%) (*n = 186*)	Intercepted potential ADEs, *n* (%) (*n = 23*)	Non-intercepted potential ADEs, *n* (%) (*n = 163*)
Antibiotics	10 (1.0)	0 (0)	10 (1.3)	2 (1.1)	0 (0)	2 (1.2)
Antihypertensives	14 (1.5)	3 (1.8)	11 (1.4)	7 (3.8)	1 (4.3)	6 (3.7)
Cardiovascular drugs	8 (0.8)	1 (0.6)	7 (0.9)	12 (6.5)	2 (8.7)	10 (6.1)
Anticoagulants	9 (0.9)	2 (1.2)	7 (0.9)	1 (0.5)	0 (0)	1 (0.6)
Antihyperlipidemics	1 (0.1)	0 (0)	1 (0.1)	0 (0)	0 (0)	0 (0)
Antidiabetics	10 (1.0)	2 (1.2)	8 (1.0)	9 (4.8)	1 (4.3)	8 (4.9)
Peptic ulcer drugs	1 (0.1)	0 (0)	1 (0.1)	0 (0)	0 (0)	0 (0)
Laxatives	40 (4.2)	10 (6.0)	30 (3.8)	7 (3.8)	0 (0)	7 (4.3)
NSAIDs	6 (0.6)	0 (0)	6 (0.8)	7 (3.8)	0 (0)	7 (4.3)
Antiallergic agents	2 (0.2)	0 (0)	2 (0.3)	0 (0)	0 (0)	0 (0)
Electrolytes or fluids	58 (6.1)	50 (30.1)	8 (1.0)	21 (11.3)	1 (4.3)	20 (12.3)
Chinese herbal medicines	2 (0.2)	0 (0)	2 (0.3)	0 (0)	0 (0)	0 (0)
Sedatives (benzodiazepine)	66 (6.9)	28 (16.9)	38 (4.8)	53 (28.5)	0 (0)	53 (32.5)
Sedatives (other)	15 (1.6)	4 (2.4)	11 (1.4)	5 (2.7)	1 (4.3)	4 (2.5)
Anxiolytics	31 (3.2)	6 (3.6)	25 (3.2)	5 (2.7)	2 (8.7)	3 (1.8)
Antidepressants (SSRI, SNRI, NaSSA)	58 (6.1)	2 (1.2)	56 (7.1)	4 (2.2)	3 (13.0)	1 (0.6)
Antidepressants (other)	62 (6.5)	6 (3.6)	56 (7.1)	1 (0.5)	1 (4.7)	0 (0)
Mood stabilizers	45 (4.7)	14 (8.4)	31 (3.9)	4 (2.2)	2 (8.7)	2 (1.2)
Antipsychotics (atypical)	323 (33.8)	32 (19.3)	291 (36.9)	34 (18.3)	6 (26.1)	28 (17.2)
Antipsychotics (typical)	125 (13.1)	4 (2.6)	121 (15.3)	1 (0.5)	0 (0)	1 (0.6)
Anticonvulsants	8 (0.8)	1 (0.6)	7 (0.9)	3 (1.6)	0 (0)	3 (1.8)
Anti-parkinsonian drugs	24 (2.5)	0 (0)	24 (3.0)	1 (0.5)	0 (0)	1 (0.6)
Anti-dementia medicines	5 (0.5)	0 (0)	5 (0.6)	1 (0.5)	1 (4.3)	0 (0)
Other drugs	32 (3.4)	1 (0.6)	31 (3.9)	8 (4.3)	2 (8.7)	6 (3.7)
Psychiatric drugs[a]	762 (79.8)	97 (58.4)	665 (84.3)	112 (60.2)	16 (69.6)	96 (58.9)
Non-psychiatric drugs[b]	193 (20.2)	69 (41.6)	124 (15.7)	74 (39.8)	7 (30.4)	67 (41.1)
All drugs	955 (100)	166 (100)	789 (100)	186 (100)	23 (100)	163 (100)

ADEs adverse drug events, *NSAIDs* nonsteroidal anti-inflammatory drugs, *SSRI* selective serotonin reuptake inhibitor; *SNRI* serotonin-noradrenaline reuptake inhibitor, *NaSSA* noradrenergic and specific serotonin antidepressants

[a]Psychiatric drugs include: sedatives (benzodiazepine), sedatives (other), anxiolytics, antidepressants (SSRI, SNRI, NaSSA), antidepressants (other), mood stabilizers, antipsychotics (atypical), antipsychotics (typical), anticonvulsants, anti-parkinsonian drugs and anti-dementia medicines

[b]Non-psychiatric drugs include: antibiotics, antihypertensives, cardiovascular drugs, anticoagulants, antihyperlipidemics, antidiabetics, peptic ulcer drugs, laxatives, NSAIDs, antiallergic agents, electrolytes or fluids, Chinese herbal medicines and other drugs

The reasons for the higher incidence of ADEs in the present study may result from differences inpatient characteristics between this study and the USA study. The most common diagnosis in the USA study was mood disorders (66.4 %), while schizophrenic disorder (25 %) followed by dementia (22 %) were the most common disorders in the present study. In accordance with this finding, Schmidt et al. (1984) reported a similar rate of ADRs (346 per 100 admissions) in a previous study performed in Germany in which schizophrenic disorder was the most common diagnosis (37 %) [11], and Hermesh et al. (1985) reported that elderly patients with organic brain disorders were at high risk of ADRs [12].

Differences of the medical system in the treatment of physical complications in psychiatric inpatients may be another possible reason for the discrepancy between our findings and prior reports on this topic. Patients in psychiatric settings in Japan tend to receive more extensive treatments for physical complications compared to patients in the USA, where patients with severe physical complications are commonly transferred to a general-care setting, especially in cases that require electrocardiographic monitoring or a continuous intravenous drip [7]. As a result, patients in Japanese inpatient psychiatric units may be at higher risk of ADEs and medication errors, as prescribing unfamiliar drugs is associated with

medication errors due to lack of experience and knowledge for practitioners in both psychiatric and general settings [7, 22]. In the present study, the proportion of preventable ADEs associated with non-psychiatric drugs was three times higher compared to psychiatric drugs (36 % v. 13 %, respectively), and the incidence of preventable ADEs was higher in the medical care units compared to acute and nursing care units (27.5 v. 5.1 v. 9.2 per 1000 patient-days, respectively).

Comparison to general-care settings in Japan

Compared with a previous study on ADEs in general-care settings in Japan [17], we also found a higher incidence of ADEs (42.0 v. 17.0 per 1000 patient-days) and medication errors (17.5 v. 8.7 per 1000 patient-days). The higher incidence of ADEs and medication errors in psychiatry units may result from the specific complexities of the medications used to treat psychiatric patients. Our results demonstrated that almost half of ADEs were associated with antipsychotics, which is in accordance with previous studies that also found that antipsychotics were the drug class most frequently associated with ADEs [7, 11, 13]. Antipsychotics are prescribed for many patients—not only for the treatment of schizophrenia but also for sedation in agitated patients—and they may cause a wide range of ADEs, including neurological, gastrointestinal, cardiovascular, metabolic and endocrine symptoms. The frequency and intensity of ADEs resulting from the use of antipsychotics (especially when used at high dosages for patients with severe mental disorders) may contribute to the high incidence of ADEs in psychiatric units. In addition, psychiatric patients with severe mental disorders may lack self-awareness, and as a result, they may not be able to fully report their symptoms due to ADEs to medical staff. Furthermore, if they unexpectedly refuse to take their medications, this may cause more frequent medication errors. Finally, monitoring errors may occur due to a combination of lack of experience and knowledge regarding the management of physical complications on the part of psychiatrists as well as inadequate staffing in psychiatric units [15].

Clinical implications

Psychiatrists usually regard ADEs like constipation from antipsychotics and drowsiness from sedatives as common and unavoidable consequences of medication, and believe that such ADEs seldom cause serious outcomes. However, serious ADEs are not rare, even though only a small percentage of ADEs are serious because ADEs occur frequently in medical care. According to the results of this research, life-threatening and serious ADEs accounted for 1.4 % (13 events in 12 patients) and 28 % (265 events in 124 patients) of events, respectively. Psychiatrists sometimes have to decide whether or not to continue administering medications associated with ADEs to treat patients with serious mental conditions; therefore, it is important to identify ADEs at an earlier stage to prevent serious events or to ameliorate their severity.

Moreover, as demonstrated by the results of the present study, psychiatrists were likely to make medication errors with ADEs during physical treatments, especially during the monitoring stage. This may be because psychiatrists focus on psychiatric problems and are less likely to treat physical problems, especially in psychiatric settings. Physicians usually tend to keep psychiatric inpatients at a distance, and psychiatrists in Japan may thus have to treat physical complications, with the exception of very severe physical conditions. Fragmentation of the physical and mental health systems is one of the barriers that hinders patients from receiving adequate care; [23] therefore, fixing the fragmented systems and increasing communication between physicians and psychiatrists could improve patients' physical health and minimize injury from medications among psychiatric inpatients in Japan and other countries.

Study limitation and strengths

Our study had several limitations. First, we conducted this study at one psychiatric hospital and one tertiary care teaching hospital. Therefore, our results may not represent other hospitals, although we attempted to mitigate this limitation by including both a psychiatric hospital and a tertiary care teaching hospital to represent a wide range of psychiatric settings. Second, we could not estimate the incidence and nature of ADEs and medication errors caused by doctors with other specialties in psychiatric settings because almost all medications were prescribed by psychiatrists in this study. Third, some ADEs and medication errors may have been missed, which would mean that our results underestimate the true incidence. However, we were able to precisely evaluate and collect data on confirmed incidents, especially physical symptoms due to ADEs; this was because internists with experience in the classification of ADEs as a result of previous research on this topic [17, 18] played a leading role in this study. In addition, more robust alternatives for measuring ADEs and medication errors have not yet been developed, and the approach we used is the approach that is currently used most widely, suggesting that the figures obtained in this study are the best that are currently available.

Conclusions

We found high incidences of ADEs and medication errors in general psychiatric settings and identified some risk factors for ADEs, including prescription of antipsychotics and treatment during the monitoring stage after drugs are administered. Therefore, clinicians should be

cautious in prescribing antipsychotics and while monitoring patients after administration, especially when patients are unable to report their symptoms due to a severe mental condition. Furthermore, because of the higher risk of ADEs and medication errors during the treatment of physical complications, consultation with physicians in other departments is essential when psychiatrists are considering prescribing unfamiliar medications for physical problems in their psychiatric patients.

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Availability of data and materials
We do not wish to share the datasets because only a portion of the datasets was used in the reported study, and we are going to conduct a secondary analysis using the datasets. We will share the datasets if the datasets have been entirely processed.

Authors' contributions
All authors were involved in the design of the study. NA, MS, TM, TK, KW, and JN collected the data. NA analyzed the data under the technical supervision of MS and TM. NA and JN interpreted study results, and NA wrote the first draft of the manuscript. All authors reviewed the manuscript, provided substantive intellectual contributions, and approved the final version of the manuscript for publication.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
The study was approved by the institutional review boards of the Kyoto Prefectural University of Medicine. The need for informed consent was waived because all data were collected as part of the hospitals' daily practices.

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別紙４

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