3. 急性胆管炎フローチャート

Flowchart for the management of acute cholangitis (0330_Record)

【3-4　クリニカルクエスチョンの設定】CQ1

スコープで取り上げた重要臨床課題(Key Clinical Issue)				
急性胆管炎の基本的初期治療				
CQの構成要素				
P (Patients, Problem, Population)				
性別	指定なし			
年齢	指定なし			
疾患・病態	急性胆管炎			
地理的要件	なし			
その他	なし			
I (Interventions)／C (Comparisons, Controls)のリスト				
急性胆管炎の初期治療				
O (Outcomes)のリスト				
	Outcomeの内容	益か害か	重要度	採用可否
O1			点	×
O2			点	
O3			点	
O4			点	
O5			点	
O6			点	
O7			点	
O8			点	
O9			点	
O10			点	
作成したCQ				
急性胆管炎の基本的初期治療は？				

【5-1 推奨文章案】CQ1

1. CQ

急性胆管炎の基本的初期治療は？

2. 推奨草案

原則として入院の上，胆道ドレナージ術の施行を前提として，絶食の上で十分な量の輸液，電解質の補正，抗菌薬投与，鎮痛薬投与を行う。

3. 作成グループにおける、推奨に関連する価値観や好み（検討した各アウトカム別に、一連の価値観を想定する）

急性胆管炎を対象とした初期治療についての研究は存在しないが、必要不可欠な治療であるため重要であると考えられる。

4. CQに対するエビデンスの総括（重大なアウトカム全般に関する全体的なエビデンスの強さ）

☐ A（強）　☐ B（中）　☐ C（弱）　☑ D（非常に弱い）

5. 推奨の強さを決定するための評価項目（下記の項目について総合して判定する）

推奨の強さの決定に影響する要因	判定	説明
アウトカム全般に関する全体的なエビデンスが強い ・全体的なエビデンスが強いほど推奨度は「強い」とされる可能性が高くなる。 ・逆に全体的なエビデンスが弱いほど、推奨度は「弱い」とされる可能性が高くなる。	☐ はい ☑ いいえ	
益と害のバランスが確実（コストは含まず） ・望ましい効果と望ましくない効果の差が大きければ大きいほど、推奨度が強くなる可能性が高い。 ・正味の益が小さければ小さいほど、有害事象が大きいほど、益の確実性が減じられ、推奨度が「弱い」とされる可能性が高くなる。	☑ はい ☐ いいえ	

推奨の強さに考慮すべき要因
患者の価値観や好み、負担の確実さ（あるいは相違）
正味の利益がコストや資源に十分に見合ったものかどうかなど

重症例に対する臓器サポートを除けば患者の症状緩和に有用で費用は安価である。

明らかに判定当てはまる場合「はい」とし、それ以外は、どちらとも言えないを含め「いいえ」とする

【3-4　クリニカルクエスチョンの設定】CQ2

スコープで取り上げた重要臨床課題(Key Clinical Issue)
TG13急性胆管炎フローチャートの有用性

CQの構成要素	
P (Patients, Problem, Population)	
性別	指定なし
年齢	指定なし
疾患・病態	急性胆管炎
地理的要件	なし
その他	なし

I (Interventions)／C (Comparisons, Controls)のリスト
中等症以下症例に対する早期腹腔鏡下総胆管切石術/待機的腹腔鏡下総胆管切石術

O (Outcomes)のリスト

	Outcomeの内容	益か害か	重要度	採用可否
O1	Mortality	害	8 点	○
O2	Coversion	害	8 点	○
O3	在院日数	害	8 点	○
O4			点	
O5			点	
O6			点	
O7			点	
O8			点	
O9			点	
O10			点	

作成したCQ
TG13急性胆管フローチャートは有用か？

【4-7 評価シート エビデンス総体】CQ2

診療ガイドライン	急性胆管炎
対象	総胆管結石による中等症以下の急性胆管炎
介入	早期腹腔鏡下総胆管切石術
対照	待機的腹腔鏡下総胆管切石術

エビデンスの強さはRCTは"強(A)"からスタート、観察研究は弱(C)からスタート
* 各ドメインは"高(-2)"、"中/疑い(-1)"、"低(0)"の3段階
** エビデンスの強さは"強(A)"、"中(B)"、"弱(C)"、"非常に弱(D)"の4段階
*** 重要性はアウトカムの重要性(1～9)

エビデンス総体

								リスク人数(アウトカム率)											
アウトカム	**研究デザイン/研究数**	**バイアスリスク***	**非一貫性***	**不精確***	**非直接性***	**その他(出版バイアスなど)***	**上昇要因(観察研究)***	**対照群分母**	**対照群分子**	**(%)**	**介入群分母**	**介入群分子**	**(%)**	**効果指標(種類)**	**効果指標統合値**	**信頼区間**	**エビデンスの強さ****	**重要性*****	**コメント**
Mortality	CS/2	-2	0	-1	0	0	0	76	0	0	69	0	0	N/A	N/A	N/A	非常に弱(D)	8	
Conversion	CS/2	-2	0	-1	0	0	0	76	0	0	69	0	0	N/A	N/A	N/A	非常に弱(D)	8	
Length of hospital stay	CS/2	-2	0	-1	0	0	0	76	N/A	N/A	69	N/A	N/A	N/A	N/A	N/A	非常に弱(D)	8	

コメント(該当するセルに記入)

【4-6 評価シート 観察研究】CQ2

診療ガイドライン	急性胆管炎
対象	総胆管結石による中等症以下の急性胆管炎
介入	早期腹腔鏡下総胆管切石術
対照	待機的腹腔鏡下総胆管切石術

*バイアスリスク、非直接性
　各ドメインの評価は"高(-2)"、"中/疑い(-1)"、"低(0)"の3段階
　まとめは"高(-2)"、"中(-1)"、"低(0)"の3段階でエビデンス総体に反映させる
** 上昇要因
　各項目の評価は"高(+2)"、"中(+1)"、"低(0)"の3段階
　まとめは"高(+2)"、"中(+1)"、"低(0)"の3段階でエビデンス総体に反映させる
各アウトカムごとに別紙にまとめる

アウトカム	Mortality

個別研究		バイアスリスク*							上昇要因**				非直接性*					リスク人数(アウトカム率)								
		選択バイアス	実行バイアス	検出バイアス	症例現象バイアス	その他																				
研究コード	研究デザイン	背景因子の差	ケアの差	不適切なアウトカム測定	不完全なフォローアップ	不十分な交絡の調整	その他のバイアス	まとめ	量反応関係	効果減弱交絡	効果の大きさ	まとめ	対象	介入	対照	アウトカム	まとめ	対照群分母	対照群分子	(%)	介入群分母	介入群分子	(%)	効果指標(種類)	効果指標(値)	信頼区間
Zhu2014	症例集積	-1	0	0	0	0	0	-1	0	0	0	0	-2	0	-1	0	-2	35	0	0	37	0	0	N/A	N/A	N/A
Zhu2015	症例集積	0	0	0	0	0	0	0	0	0	0	0	-2	0	0	0	-2	41	0	0	32	0	0	N/A	N/A	N/A

コメント(該当するセルに記入)

	術前臨床徴候と検査値											連続した症例でない。		早期と待機の基準なし。											
												除外症例が多い。														

【3-4　クリニカルクエスチョンの設定】CQ2.

スコープで取り上げた重要臨床課題(Key Clinical Issue)				
TG13急性胆管炎フローチャートの有用性				
CQの構成要素				
P (Patients, Problem, Population)				
性別	指定なし			
年齢	指定なし			
疾患・病態	急性胆管炎			
地理的要件	なし			
その他	なし			
I (Interventions)／C (Comparisons, Controls)のリスト				
緊急または早期胆管ドレナージ/待機的ドレナージまたはドレナージなし				
O (Outcomes)のリスト				
	Outcomeの内容	益か害か	重要度	採用可否
O1	Mortality	害	8 点	○
O2				
O3				
O4			点	
O5			点	
O6			点	
O7			点	
O8			点	
O9			点	
O10			点	
作成したCQ				
TG13急性胆管フローチャートは有用か？				

【4-7 評価シート エビデンス総体】CQ2

診療ガイドライン	急性胆管炎
対象	軽症急性胆管炎
介入	早期胆管ドレナージ
対照	待機的ドレナージまたはドレナージなし

エビデンスの強さはRCTは"強(A)"からスタート、観察研究は弱(C)からスタート
* 各ドメインは"高(-2)"、"中/疑い(-1)"、"低(0)"の3段階
** エビデンスの強さは"強(A)"、"中(B)"、"弱(C)"、"非常に弱(D)"の4段階
*** 重要性はアウトカムの重要性(1～9)

エビデンス総体

								リスク人数(アウトカム率)											
アウトカム	**研究デザイン/研究数**	**バイアスリスク***	**非一貫性***	**不精確***	**非直接性***	**その他(出版バイアスなど)***	**上昇要因(観察研究)***	**対照群分母**	**対照群分子**	**(%)**	**介入群分母**	**介入群分子**	**(%)**	**効果指標(種類)**	**効果指標統合値**	**信頼区間**	**エビデンスの強さ****	**重要性*****	**コメント**
Mortality	CS/1	0	0	0	0	0	0	1082	15	1.7	1441	16	0				弱(C)	8	軽症例には早期胆管ドレナージは必要でないというエビデンスになり

コメント(該当するセルに記入)

【4-6 評価シート 観察研究】CQ2

診療ガイドライン	急性胆管炎
対象	総胆管結石による中等症以下の急性胆管炎
介入	早期腹腔鏡下総胆管切石術
対照	待機的腹腔鏡下総胆管切石術

*バイアスリスク、非直接性
　各ドメインの評価は"高(-2)"、"中/疑い(-1)"、"低(0)"の3段階
　まとめは"高(-2)"、"中(-1)"、"低(0)"の3段階でエビデンス総体に反映させる
** 上昇要因
　各項目の評価は"高(+2)"、"中(+1)"、"低(0)"の3段階
　まとめは"高(+2)"、"中(+1)"、"低(0)"の3段階でエビデンス総体に反映させる
各アウトカムごとに別紙にまとめる

アウトカム	Comversion

個別研究		バイアスリスク*							上昇要因**				非直接性*					リスク人数(アウトカム率)								
		選択バイアス	実行バイアス	検出バイアス	症例現象バイアス	その他																				
研究コード	研究デザイン	背景因子の差	ケアの差	不適切なアウトカム測定	不完全なフォローアップ	不十分な交絡の調整	その他のバイアス	まとめ	量反応関係	効果減弱交絡	効果の大きさ	まとめ	対象	介入	対照	アウトカム	まとめ	対照群分母	対照群分子	(%)	介入群分母	介入群分子	(%)	効果指標(種類)	効果指標(値)	信頼区間
Zhu2014	症例集積	-1	0	0	0	0	0	-1	0	0	0	0	-2	0	-1	0	-2	35	0	0	37	0	0	N/A	N/A	N/A
Zhu2015	症例集積	0	0	0	0	0	0	0	0	0	0	0	-2	0	0	0	-2	41	0	0	32	0	0	N/A	N/A	N/A

コメント(該当するセルに記入)

	術前臨床徴候と検査値											連続した症例でない。		早期と待機の基準なし											
												除外症例が多い。														

【4-7 評価シート エビデンス総体】CQ2

診療ガイドライン	急性胆管炎
対象	中等症急性胆管炎
介入	早期胆管ドレナージ
対照	待機的ドレナージまたはドレナージなし

エビデンスの強さはRCTは"強(A)"からスタート、観察研究は弱(C)からスタート
* 各ドメインは"高(-2)"、"中/疑い(-1)"、"低(0)"の3段階
** エビデンスの強さは"強(A)"、"中(B)"、"弱(C)"、"非常に弱(D)"の4段階
*** 重要性はアウトカムの重要性(1～9)

エビデンス総体

								リスク人数(アウトカム率)											
アウトカム	**研究デザイン/研究数**	**バイアスリスク***	**非一貫性***	**不精確***	**非直接性***	**その他(出版バイアスなど)***	**上昇要因(観察研究)***	**対照群分母**	**対照群分子**	**(%)**	**介入群分母**	**介入群分子**	**(%)**	**効果指標(種類)**	**効果指標統合値**	**信頼区間**	**エビデンスの強さ****	**重要性*****	**コメント**
Mortality	CS/1	0	0	0	0	0	0	748	31	4.1	1277	22	1.7				弱(C)	8	中等症例には早期胆管ドレナージが必要であるというエビデンスになり得る。

コメント(該当するセルに記入)

【4-6 評価シート 観察研究】CQ2

診療ガイドライン	急性胆管炎
対象	総胆管結石による中等症以下の急性胆管炎
介入	早期腹腔鏡下総胆管切石術
対照	待機的腹腔鏡下総胆管切石術

*バイアスリスク、非直接性
　各ドメインの評価は"高(-2)"、"中/疑い(-1)"、"低(0)"の3段階
　まとめは"高(-2)"、"中(-1)"、"低(0)"の3段階でエビデンス総体に反映させる
** 上昇要因
　各項目の評価は"高(+2)"、"中(+1)"、"低(0)"の3段階
　まとめは"高(+2)"、"中(+1)"、"低(0)"の3段階でエビデンス総体に反映させる
各アウトカムごとに別紙にまとめる

アウトカム	Length of hospital stay
個別研究	

		バイアスリスク*							上昇要因**				非直接性*					リスク人数(アウトカム率)								
		選択バイアス	実行バイアス	検出バイアス	症例現象バイアス	その他																				
研究コード	**研究デザイン**	**背景因子の差**	**ケアの差**	**不適切なアウトカム測定**	**不完全なフォローアップ**	**不十分な交絡の調整**	**その他のバイアス**	**まとめ**	**量反応関係**	**効果減弱交絡**	**効果の大きさ**	**まとめ**	**対象**	**介入**	**対照**	**アウトカム**	**まとめ**	**対照群分母**	**対照群分子**	**(%)**	**介入群分母**	**介入群分子**	**(%)**	**効果指標(種類)**	**効果指標(値)**	**信頼区間**
Zhu2014	症例集積	-1	0	0	0	0	0	-1	0	0	0	0	-2	0	-1	0	-2	35	N/A	N/A	37	N/A	N/A	N/A	N/A	N/A
Zhu2015	症例集積	0	0	0	0	0	0	0	0	0	0	0	-2	0	0	0	-2	41	N/A	N/A	32	N/A	N/A	N/A	N/A	N/A

コメント(該当するセルに記入)

	術前臨床徴候と検査値											連続した症例でない。		早期と待機の基準なし											
												除外症例														

【4-7 評価シート エビデンス総体】CQ2

診療ガイドライン	急性胆管炎
対象	重症急性胆管炎
介入	早期胆管ドレナージ
対照	待機的ドレナージまたはドレナージなし

エビデンスの強さはRCTは"強(A)"からスタート、観察研究は弱(C)からスタート
* 各ドメインは"高(-2)"、"中/疑い(-1)"、"低(0)"の3段階
** エビデンスの強さは"強(A)"、"中(B)"、"弱(C)"、"非常に弱(D)"の4段階
*** 重要性はアウトカムの重要性(1～9)

エビデンス総体

								リスク人数(アウトカム率)											
アウトカム	**研究デザイン/研究数**	**バイアスリスク***	**非一貫性***	**不精確***	**非直接性***	**その他(出版バイアスなど)***	**上昇要因(観察研究)***	**対照群分母**	**対照群分子**	**(%)**	**介入群分母**	**介入群分子**	**(%)**	**効果指標(種類)**	**効果指標統合値**	**信頼区間**	**エビデンスの強さ****	**重要性*****	**コメント**
Mortality	CS/1	0	0	0	0	0	0	739	39	5.3	776	35	4.5				弱(C)	8	

コメント(該当するセルに記入)

【4-6 評価シート 観察研究】CQ2

診療ガイドライン	急性胆管炎
対象	軽症急性胆管炎
介入	早期胆管ドレナージ
対照	待機的ドレナージまたはドレナージなし

*バイアスリスク、非直接性
　各ドメインの評価は"高(-2)"、"中/疑い(-1)"、"低(0)"の3段階
　まとめは"高(-2)"、"中(-1)"、"低(0)"の3段階でエビデンス総体に反映させる
** 上昇要因
　各項目の評価は"高(+2)"、"中(+1)"、"低(0)"の3段階
　まとめは"高(+2)"、"中(+1)"、"低(0)"の3段階でエビデンス総体に反映させる
各アウトカムごとに別紙にまとめる

アウトカム	Mortality

個別研究		**バイアスリスク***							**上昇要因****				**非直接性***					**リスク人数(アウトカム率)**								
		選択バイアス	**実行バイアス**	**検出バイアス**	**症例現象バイアス**	**その他**																				
研究コード	**研究デザイン**	**背景因子の差**	**ケアの差**	**不適切なアウトカム測定**	**不完全なフォローアップ**	**不十分な交絡の調整**	**そのほかのバイアス**	**まとめ**	**量反応関係**	**効果減弱交絡**	**効果の大きさ**	**まとめ**	**対象**	**介入**	**対照**	**アウトカム**	**まとめ**	**対照群分母**	**対照群分子**	**(%)**	**介入群分母**	**介入群分子**	**(%)**	**効果指標(種類)**	**効果指標(値)**	**信頼区間**
Kiriyama	症例集積	-1	-1	0	0	0	0	-1	0	0	0	0	0	0	0	0	0	1082	15	1.7	1441	16	0			

コメント(該当するセルに記入)

	検討されていない	検討されていない																								

【4-6 評価シート 観察研究】CQ2

診療ガイドライン	急性胆管炎
対象	中等症急性胆管炎
介入	早期胆管ドレナージ
対照	待機的ドレナージまたはドレナージなし

*バイアスリスク、非直接性
　各ドメインの評価は"高(-2)"、"中/疑い(-1)"、"低(0)"の3段階
　まとめは"高(-2)"、"中(-1)"、"低(0)"の3段階でエビデンス総体に反映させる
** 上昇要因
　各項目の評価は"高(+2)"、"中(+1)"、"低(0)"の3段階
　まとめは"高(+2)"、"中(+1)"、"低(0)"の3段階でエビデンス総体に反映させる
各アウトカムごとに別紙にまとめる

アウトカム	Mortality

個別研究		**バイアスリスク***							**上昇要因****				**非直接性***					**リスク人数(アウトカム率)**								
研究コード	**研究デザイン**	**選択バイアス**	**実行バイアス**	**検出バイアス**	**症例現象バイアス**	**その他**		**まとめ**	**量反応関係**	**効果減弱交絡**	**効果の大きさ**	**まとめ**	**対象**	**介入**	**対照**	**アウトカム**	**まとめ**	**対照群分母**	**対照群分子**	**(%)**	**介入群分母**	**介入群分子**	**(%)**	**効果指標(種類)**	**効果指標(値)**	**信頼区間**
		背景因子の差	**ケアの差**	**不適切なアウトカム測定**	**不完全なフォローアップ**	**不十分な交絡の調整**	**そのほかのバイアス**																			
Kiriyama	症例集積	-1	-1	0	0	0	0	-1	0	0	0	0	0	0	0	0	0	748	31	4.1	1277	22	1.7			

コメント(該当するセルに記入)

	検討されていない	検討されていない																								

【4-6 評価シート 観察研究】CQ2.

診療ガイドライン	急性胆管炎
対象	重症急性胆管炎
介入	緊急胆管ドレナージ
対照	待機的ドレナージまたはドレナージなし

*バイアスリスク、非直接性
　各ドメインの評価は"高(-2)"、"中/疑い(-1)"、"低(0)"の3段階
　まとめは"高(-2)"、"中(-1)"、"低(0)"の3段階でエビデンス総体に反映させる
** 上昇要因
　各項目の評価は"高(+2)"、"中(+1)"、"低(0)"の3段階
　まとめは"高(+2)"、"中(+1)"、"低(0)"の3段階でエビデンス総体に反映させる
各アウトカムごとに別紙にまとめる

アウトカム	Mortality

個別研究		バイアスリスク*							上昇要因**				非直接性*					リスク人数(アウトカム率)								
		選択バイアス	実行バイアス	検出バイアス	症例現象バイアス	その他																				
研究コード	研究デザイン	背景因子の差	ケアの差	不適切なアウトカム測定	不完全なフォローアップ	不十分な交絡の調整	その他のバイアス	まとめ	量反応関係	効果減弱交絡	効果の大きさ	まとめ	対象	介入	対照	アウトカム	まとめ	対照群分母	対照群分子	(%)	介入群分母	介入群分子	(%)	効果指標(種類)	効果指標(値)	信頼区間
Kiriyama	症例集積	-1	-1	0	0	0	0	-1	0	0	0	0	0	0	0	0	0	739	39	5.3	776	35	4.5			

コメント(該当するセルに記入)

	検討されていない	検討されていない																								

【5-1 推奨文章案】CQ2

1. CQ

TG13急性胆管フローチャートは有用か？

2. 推奨草案

フローチャートに従い治療を進めるべきである。

3. 作成グループにおける、推奨に関連する価値観や好み（検討した各アウトカム別に、一連の価値観を想定する）

フローチャートそのものに対するエビデンスは少ないが、早期の胆管ドレナージは広く行われているし、救命率の向上に寄与し得ると考える。

4. CQに対するエビデンスの総括（重大なアウトカム全般に関する全体的なエビデンスの強さ）

☐ A（強）　☐ B（中）　☐ C（弱）　☑ D（非常に弱い）

5. 推奨の強さを決定するための評価項目（下記の項目について総合して判定する）

推奨の強さの決定に影響する要因	判定	説明
アウトカム全般に関する全体的なエビデンスが強い ・全体的なエビデンスが強いほど推奨度は「強い」とされる可能性が高くなる。 ・逆に全体的なエビデンスが弱いほど、推奨度は「弱い」とされる可能性が高くなる。	☐ はい ☑ いいえ	
益と害のバランスが確実（コストは含まず） ・望ましい効果と望ましくない効果の差が大きければ大きいほど、推奨度が強くなる可能性が高い。 ・正味の益が小さければ小さいほど、有害事象が大きいほど、益の確実性が減じられ、推奨度が「弱い」とされる可能性が高くなる。	☑ はい ☐ いいえ	

推奨の強さに考慮すべき要因
患者の価値観や好み、負担の確実さ（あるいは相違）
正味の利益がコストや資源に十分に見合ったものかどうかなど

一般的に広く行われている治療法を提示しているので、患者の負担は強くはないし費用面でも問題はないと考えられる。

明らかに判定当てはまる場合「はい」とし、それ以外は、どちらとも言えないを含め「いいえ」とする

【3-4　クリニカルクエスチョンの設定】CQ3

スコープで取り上げた重要臨床課題(Key Clinical Issue)
急性胆管炎バンドルの有用性

CQの構成要素	
P (Patients, Problem, Population)	
性別	指定なし
年齢	指定なし
疾患・病態	急性胆管炎
地理的要件	なし
その他	なし

I (Interventions)／C (Comparisons, Controls)のリスト
バンドルの遵守率高/バンドルの遵守率低

O (Outcomes)のリスト

	Outcomeの内容	益か害か	重要度	採用可否
O1	Mortality	害	8 点	○
O2	Length of hospital stay	害	8 点	○
O3	医療費	害	8 点	○
O4			点	
O5			点	
O6			点	
O7			点	
O8			点	
O9			点	
O10			点	

作成したCQ
急性胆管炎バンドルは有用か？

【4-6 評価シート 観察研究】CQ3

診療ガイドライン	急性胆管炎
対象	急性胆管炎
介入	高TG07推奨治療遵守スコア
対照	低TG07推奨治療遵守スコア

*バイアスリスク、非直接性
　各ドメインの評価は"高(-2)"、"中/疑い(-1)"、"低(0)"の3段階
　まとめは"高(-2)"、"中(-1)"、"低(0)"の3段階でエビデンス総体に反映させる
** 上昇要因
　各項目の評価は"高(+2)"、"中(+1)"、"低(0)"の3段階
　まとめは"高(+2)"、"中(+1)"、"低(0)"の3段階でエビデンス総体に反映させる
各アウトカムごとに別紙にまとめる

アウトカム	Mortality

個別研究		バイアスリスク*							上昇要因**				非直接性*					リスク人数(アウトカム率)								
		選択バイアス	実行バイアス	検出バイアス	症例現象バイアス	その他																				
研究コード	研究デザイン	背景因子の差	ケアの差	不適切なアウトカム測定	不完全なフォローアップ	不十分な交絡の調整	その他のバイアス	まとめ	量反応関係	効果減弱交絡	効果の大きさ	まとめ	対象	介入	対照	アウトカム	まとめ	対照群分母	対照群分子	(%)	介入群分母	介入群分子	(%)	効果指標(種類)	効果指標(値)	信頼区間
Murata	症例集積	0	0	0	0	0	0	0	0	0	0	0	0	-1	-1	-2	-2	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	

コメント(該当するセルに記入)

													例数が不明。	例数が不明。	推奨治療はbundleとは異なる。											

【4-6 評価シート 観察研究】CQ3

診療ガイドライン	急性胆管炎
対象	急性胆管炎
介入	高TG07推奨治療遵守スコア
対照	低TG07推奨治療遵守スコア

*バイアスリスク、非直接性
　各ドメインの評価は"高(-2)"、"中/疑い(-1)"、"低(0)"の3段階
　まとめは"高(-2)"、"中(-1)"、"低(0)"の3段階でエビデンス総体に反映させる
** 上昇要因
　各項目の評価は"高(+2)"、"中(+1)"、"低(0)"の3段階
　まとめは"高(+2)"、"中(+1)"、"低(0)"の3段階でエビデンス総体に反映させる
各アウトカムごとに別紙にまとめる

アウトカム	Length of hospital stay

個別研究		バイアスリスク*							上昇要因**				非直接性*					リスク人数(アウトカム率)								
		選択バイアス	実行バイアス	検出バイアス	症例現象バイアス	その他																				
研究コード	研究デザイン	背景因子の差	ケアの差	不適切なアウトカム測定	不完全なフォローアップ	不十分な交絡の調整	その他のバイアス	まとめ	量反応関係	効果減弱交絡	効果の大きさ	まとめ	対象	介入	対照	アウトカム	まとめ	対照群分母	対照群分子	(%)	介入群分母	介入群分子	(%)	効果指標(種類)	効果指標(値)	信頼区間
村田	症例集積	0	0	0	0	0	0	0	0	0	0	0	0	-1	-1	-2	-2	39256	N/A	N/A	21586	N/A	N/A	日数	N/A	

コメント(該当するセルに記入)

													例数が不明。	例数が不明。	推奨治療はbundleとは異なる。									両群の重度別しか示されていない。	

【4-6 評価シート 観察研究】CQ3

診療ガイドライン	急性胆管炎
対象	急性胆管炎
介入	高TG07推奨治療遵守スコア
対照	低TG07推奨治療遵守スコア

*バイアスリスク、非直接性
　各ドメインの評価は"高(-2)"、"中/疑い(-1)"、"低(0)"の3段階
　まとめは"高(-2)"、"中(-1)"、"低(0)"の3段階でエビデンス総体に反映させる
** 上昇要因
　各項目の評価は"高(+2)"、"中(+1)"、"低(0)"の3段階
　まとめは"高(+2)"、"中(+1)"、"低(0)"の3段階でエビデンス総体に反映させる
各アウトカムごとに別紙にまとめる

アウトカム	平均医療費

個別研究		**バイアスリスク***							**上昇要因****				**非直接性***					**リスク人数(アウトカム率)**								
		選択バイアス	**実行バイアス**	**検出バイアス**	**症例現象バイアス**	**その他**																				
研究コード	**研究デザイン**	**背景因子の差**	**ケアの差**	**不適切なアウトカム測定**	**不完全なフォローアップ**	**不十分な交絡の調整**	**その他のバイアス**	**まとめ**	**量反応関係**	**効果減弱交絡**	**効果の大きさ**	**まとめ**	**対象**	**介入**	**対照**	**アウトカム**	**まとめ**	**対照群分母**	**対照群分子**	**(%)**	**介入群分母**	**介入群分子**	**(%)**	**効果指標(種類)**	**効果指標(値)**	**信頼区間**
村田	症例集積	0	0	0	0	0	0	0	0	0	0	0	0	-1	-1	-2	-2	####	N/A	N/A	####	N/A	N/A	平均医療費	N/A	

コメント(該当するセルに記入)

														例数が不明。	例数が不明。	推奨治療はbundleとは異なる。									群重度別しか示されていない。	

【4-7 評価シート エビデンス総体】CQ3

診療ガイドライン	急性胆管炎
対象	急性胆管炎
介入	高TG07推奨治療遵守スコア
対照	低TG07推奨治療遵守スコア

エビデンスの強さはRCTは"強(A)"からスタート、観察研究は弱(C)からスタート
* 各ドメインは"高(-2)"、"中/疑い(-1)"、"低(0)"の3段階
** エビデンスの強さは"強(A)"、"中(B)"、"弱(C)"、"非常に弱(D)"の4段階
*** 重要性はアウトカムの重要性(1～9)

エビデンス総体

								リスク人数(アウトカム率)											
アウトカム	**研究デザイン/研究数**	**バイアスリスク***	**非一貫性***	**不精確***	**非直接性***	**その他(出版バイアスなど)***	**上昇要因(観察研究)***	**対照群分母**	**対照群分子**	**(%)**	**介入群分母**	**介入群分子**	**(%)**	**効果指標(種類)**	**効果指標統合値**	**信頼区間**	**エビデンスの強さ****	**重要性*****	**コメント**
Mortality	CS/1	0	0	-2	-2	0	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	非常に弱(D)	8	
Length of hospital stay	CS/1	0	0	-2	-2	0	0	####	N/A	N/A	####	N/A	N/A	日数	N/A	N/A	非常に弱(D)	8	
医療費	CS/1	0	0	-2	-2	0	0	####	N/A	N/A	####	N/A	N/A	医療費	N/A	N/A	非常に弱(D)	8	

コメント(該当するセルに記入)

				重症度判定基準に基づいていない。	推奨治療はbundleとは異なる。														
				重症度判定基準に基づいていない。	推奨治療はbundleとは異なる。														
				重症度判定基準に基づいていない。	推奨治療はbundleとは異なる。														

【5-1 推奨文章案】CQ3

1. CQ

TG13急性胆管炎バンドルは有用か？

2. 推奨草案

急性胆管炎バンドルに従い治療を進めるべきである。

3. 作成グループにおける、推奨に関連する価値観や好み（検討した各アウトカム別に、一連の価値観を想定する）

バンドルそのものに対するエビデンスは少ないが、広く日常臨床で行われている診断・治療法について列挙されており、遵守するべきと考えられる。

4. CQに対するエビデンスの総括（重大なアウトカム全般に関する全体的なエビデンスの強さ）

☐ A（強）　☐ B（中）　☐ C（弱）　☑ D（非常に弱い）

5. 推奨の強さを決定するための評価項目（下記の項目について総合して判定する）

推奨の強さの決定に影響する要因	判定	説明
アウトカム全般に関する全体的なエビデンスが強い ・全体的なエビデンスが強いほど推奨度は「強い」とされる可能性が高くなる。 ・逆に全体的なエビデンスが弱いほど、推奨度は「弱い」とされる可能性が高くなる。	☐ はい ☑ いいえ	
益と害のバランスが確実（コストは含まず） ・望ましい効果と望ましくない効果の差が大きければ大きいほど、推奨度が強くなる可能性が高い。 ・正味の益が小さければ小さいほど、有害事象が大きいほど、益の確実性が減じられ、推奨度が「弱い」とされる可能性が高くなる。	☑ はい ☐ いいえ	

推奨の強さに考慮すべき要因
患者の価値観や好み、負担の確実さ（あるいは相違）
正味の利益がコストや資源に十分に見合ったものかどうかなど

一般的に広く行われている治療法を提示しているので、患者の負担は強くはないし費用面でも問題はないと考えられる。

明らかに判定当てはまる場合「はい」とし、それ以外は、どちらとも言えないを含め「いいえ」とする

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ORIGINAL ARTICLE

Evaluation of compliance with the Tokyo Guidelines for the management of acute cholangitis based on the Japanese administrative database associated with the Diagnosis Procedure Combination system

Atsuhiko Murata · Shinya Matsuda · Kazuaki Kuwabara · Yoshihisa Fujino · Tatsuhiko Kubo · Kenji Fujimori · Hiromasa Horiguchi

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Abstract
Background/purpose We aimed to evaluate compliance with the clinical practice guidelines for acute cholangitis (Tokyo Guidelines) using the Japanese administrative database associated with the Diagnosis Procedure Combination (DPC) system.
Methods We collected database data from 60,842 acute cholangitis patients, examining 10 recommendations in the Tokyo Guidelines. We counted how many recommendations had been complied with for every patient. The patient compliance score was defined as the rate of compliance with these recommendations (score $0 = 0\%$ to score $10 = 100\%$). An aggregated patient compliance score was measured according to the severity of acute cholangitis. Severity was categorized as grade I (mild cholangitis; $n = 49{,}630$), grade II (moderate cholangitis; $n = 10{,}444$), and grade III (severe cholangitis; $n = 768$).
Results The mean patient compliance score was significantly higher for patients with grade III than for those with grades II and I (7.6 ± 2.1 vs. 6.5 ± 3.0 vs. 2.9 ± 0.9, $p < 0.001$, respectively). Multiple linear regression analysis revealed that the severity of acute cholangitis was the parameter most significantly associated with the patient compliance score. The standardized coefficient of grade III was higher than that of grade II (0.657 vs. 0.248, $p < 0.001$).
Conclusions Compliance with the Tokyo Guidelines became higher in accordance with the severity of acute cholangitis.

Keywords Acute cholangitis · Tokyo Guidelines · Compliance · Diagnosis Procedure Combination (DPC)

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Introduction

Acute cholangitis is an infectious disease of the biliary tract with a wide spectrum of symptoms. Severity ranges from a mild form with fever and jaundice, to a severe form with septic shock [1, 2]. Initial medical treatment with hydration and antimicrobial therapy remains the mainstay of therapy for acute cholangitis. However, biliary decompression should be performed early in the course of the illness, after hydration and antimicrobial therapy, if the patient's condition has not improved or has worsened [1, 2]. In such cases, endoscopic retrograde biliary drainage (ERBD) or percutaneous transhepatic cholangial drainage (PTCD) have been useful procedures for biliary decompression [3–5].

To establish standardization of these treatments, clinical practice guidelines for acute cholangitis (Tokyo Guidelines) have been prepared in Japan [6–15]. The Tokyo

Guidelines are based on the best available evidence for all issues, providing information about recommended examinations and treatments for the disease [6]. Therefore, it is reasonable that the Tokyo Guidelines are useful for the treatment of acute cholangitis, and they are widely accepted by many Japanese doctors who have engaged in internal medicine, gastroenterology, emergency medicine, and surgery.

However, no studies have examined how often the Tokyo Guidelines have been complied with in actual medical treatment for acute cholangitis. To investigate this, we analyzed compliance with the Tokyo Guidelines for acute cholangitis, using the Japanese administrative database associated with the Diagnosis Procedure Combination (DPC) system.

Methods

Study setting

We selected 61,188 patients with acute cholangitis from 829 DPC participating hospitals (82 academic and 747 community hospitals) between April and December in 2008. These hospitals are scattered throughout Japan and play a leading role in providing acute-care medicine, advancing medical research, and educating students and residents [16–18]. The principal diagnosis of acute cholangitis was recorded using the International Classification of Diseases and Injuries (ICD)-10th code edition. In the present analysis, acute cholangitis was defined as code K830 in the ICD-10th code edition. For this analysis, we excluded 346 patients aged 15 years and less because the causes of pediatric acute biliary tract infections are quite different from those of adult acute biliary tract infections (e.g., congenital biliary atresia or dilatation after liver transplantation or pancreaticobiliary maljunction) [14].

The research protocol of the study was approved by The Ethics Committee of Medical Care and Research of the University of Occupational and Environmental Health, Kitakyushu, Japan.

Selected recommendations and severity of acute cholangitis

Selected recommendations for acute cholangitis are shown in Table 1. There were ten recommendations [seven items in recommendation A (based on good available evidence) and three items in recommendation B (based on moderate available evidence)] [12, 13]. In the Tokyo Guidelines, the severity of acute cholangitis has been defined as follows: grade I (mild acute cholangitis that responds to the initial medical treatment such as hydration or antimicrobial therapy), grade II (moderate acute cholangitis that does not respond to the initial medical treatment and requires biliary drainage), and grade III (acute cholangitis that requires not only the initial medical treatment and biliary drainage, but also organ support). We used the above definitions to classify grades of the disease by way of the treatment used for each patient. For example, grade I was assigned to cases that required hydration or intravenous/oral antimicrobial therapy, either alone or in combination. Patients who also required either ERBD or PTCD were categorized as grade II. Grade III was assigned to patients critically ill with acute cholangitis who had also required either ventilation or hemodiafiltration, or a vasopressor such as dopamine or dobutamine. These classifications were confirmed for every patient using the DPC database, not by self-report.

Study variables

Study variables used were age, sex, hospital type, chronic comorbid conditions, use of ambulance and intensive care unit (ICU), hospital length of stay (LOS), in-hospital

Table 1 Selected recommendations for acute cholangitis in the Tokyo Guidelines

Recommendation A
(1) Antimicrobial agents should be administered intravenously to patients diagnosed as having acute cholangitis
(2) Antimicrobial drugs should be selected according to the severity of acute cholangitis
(3) Biliary penetration should be considered in the selection of antimicrobial agents in acute cholangitis
(4) For patients with mild (grade I) acute cholangitis, the duration of antimicrobial therapy could be shorter (2 or 3 days)
(5) For patients with moderate (grade II) or severe (grade III) acute cholangitis, antimicrobial agents should be administered for a minimum duration of 5–7 days
(6) Endoscopic biliary drainage should be selected for biliary decompression
(7) Patients with acute cholangitis, especially those with severe (grade III) disease, should have immediate biliary drainage
Recommendation B
(8) Bile cultures should be performed at all available opportunities
(9) Blood cultures should be performed at all available opportunities
(10) Cholecystectomy is indicated after the resolution of acute cholangitis

mortality, frequency and duration of intravenous antimicrobial therapy, kinds of intravenous antimicrobial drugs, ERBD and PTCD (including immediate biliary drainage), bile and blood culture, and cholecystectomy. We used the Charlson comorbidity index (CCI) to assess the severity of chronic comorbid conditions. For comparative purposes in regard to the severity of comorbid conditions, the CCI score was categorized into three groups: 0 (mild), 1 (moderate), and 2 or more (severe) [19]. Immediate biliary drainage was identified as biliary drainage that had been performed within 2 days after admission, as described in a previous study [20].

Main outcome and statistical analysis

We counted the number of recommendations that had been complied with for each patient. Compliance in grade I cases was calculated using six recommendations (items 1–4 and 9–10 in Table 1), while compliance in grade II and III cases was calculated using nine recommendations (items 1–3 and 5–10 in Table 1). In this study, each patient's score was defined as the rate of compliance with the recommendations (where "0" represents 0% compliance with the recommendations and "10" represents 100% compliance). The calculated score was rounded off to the nearest integer.

The proportions for all categorical patient data in this study were compared using the χ^2 test, analysis of variance (ANOVA), and the Kruskal–Wallis test for continuous variables. Patient compliance with the Tokyo Guidelines was evaluated according to the severity of acute cholangitis using the patient compliance score. In addition, we used multiple linear regression models to determine the individual effect of disease severity on the patient compliance score. We addressed potential confounding due to variation in the case mix by controlling for the severity of chronic comorbid conditions and additional variables related to the patient's compliance score, such as hospital type, age, sex, use of ambulance, and CCI. A value of $p < 0.05$ was considered significant. Statistical analysis was performed using the STATA statistical software package version 9.0 (Stata, College Station, TX, USA).

Results

We examined a total of 60,842 patients (49,630 patients in grade I, 10,444 patients in grade II, and 768 patients in grade III) at 829 DPC participating hospitals. The median patient age was significantly higher in grade III patients than in patients in grades I and II (66.6 ± 15.6 years in grade I vs. 73.1 ± 13.3 years in grade II vs. 75.4 ± 11.4 years in grade III). The proportion of male patients was highest in grade II, whereas the use of ambulance and use of the ICU were significantly higher in grade III than in grades I and II. Grade I included more patients with no chronic comorbid conditions (56.4%) than grades II (53.3%) and III (48.4%). Significant variation of mean LOS was observed between grades (14.6 ± 14.2 days in grade I vs. 25.0 ± 21.5 days in grade II vs. 36.0 ± 30.4 days in grade III). Grade III had significantly higher mortality than grades I and II (14.3 vs. 2.1 vs. 4.6%, respectively). There were statistically significant differences between severity categories across a number of independent variables (Table 2).

Intravenous antimicrobial therapy was administered in a significantly lower proportion of patients in grade I than in those in grades II and III (20.8 vs. 92.9 vs. 98.8%,

Table 2 Clinical characteristics and presentations of patients according to severity criteria

Grades of acute cholangitis	Grade I (mild)	Grade II (moderate)	Grade III (severe)	*p* value
Patients (*n*)	49,630	10,444	768	
Mean age [years, (SD)]	66.6 (15.6)	73.1 (13.3)	75.4 (11.4)	<0.001[a]
Male sex (%)	52.8	58.0	57.7	<0.001[b]
Use of ambulance (%)	9.3	13.1	13.3	<0.001[b]
Use of intensive care unit (%)	2.4	2.1	10.4	<0.001[b]
Charlson comorbidity index (%)				
0	56.4	53.3	48.4	<0.001[b]
1	14.0	14.0	13.6	
2 or more	29.6	32.8	38.0	
Length of stay [days, (SD)]	14.6 (14.2)	25.0 (21.5)	36.0 (30.4)	<0.001[c]
In-hospital mortality (%)	2.1	4.6	14.3	<0.001[b]

[a] *p* value was derived from analysis of variance (ANOVA)

[b] *p* values were derived from the χ^2 test

[c] *p* value was derived from the Kruskal–Wallis test

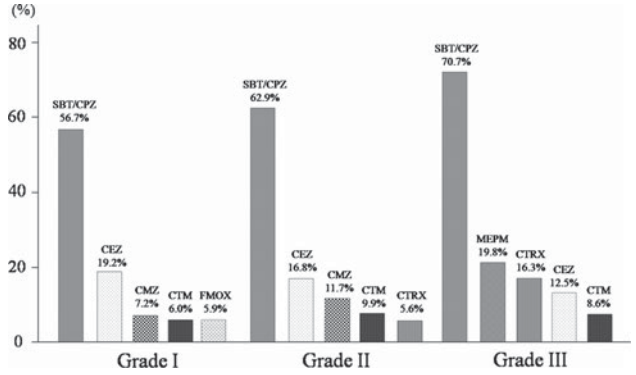

Fig. 1 Top five intravenous antimicrobial drugs according to severity of acute cholangitis. *SBT/CPZ* sulbactam/cefoperazone, *CEZ* cefazoline, *CMZ* cefmetazole, *CTM* cefotiam, *FMOX* flomoxef, *CTRX* ceftriaxone, *MEPM* meropenem

$p < 0.001$, respectively). The use of recommended antimicrobial drugs was highest in grade III, while the use of antimicrobial drugs with good biliary penetration was highest in grade II. Several antimicrobial drugs are available for the treatment of acute cholangitis, and sulbactam/cefoperazone (SBT/CPZ) was used e most often in all grades. However, in grades I and II, a higher proportion of first- and second-generation cephalosporins was used [such as cefazoline (CEZ), cefmetazole (CMZ), cefotiam (CTM), and FMOX (flomoxef)], while meropenem (MEPM) and third-generation cephalosporins [such as ceftriaxone (CTRX)] were more frequently used for patients in grade III (Fig. 1). The recommended duration of antimicrobial therapy showed more compliance in grade III (98.2%) than in grade I (81.0%) and grade II (92.3%). Endoscopic and immediate biliary drainage were performed significantly more often in grade III than in grade II (94.1 vs. 75.8%, and 52.4 vs. 36.7%, $p < 0.001$, respectively). Both bile and blood culture were also performed significantly more often in grade III than in grade II or grade I. However, patients in grade I were more likely to undergo cholecystectomy (40.2%) than those in grade II (30.7%) and grade III (12.1%) (Table 3).

The mean patient compliance score was significantly higher for patients in grade III than those in grades II and I (7.6 ± 2.1 vs. 6.5 ± 3.0 vs. 2.9 ± 0.9, $p < 0.001$, respectively) (Fig. 2). After adjusting for the potential confounding effects of demographic and clinical variables, the patient compliance score was most significantly associated with the parameter of severity. The standardized coefficient of grade III was higher than that of grade II (0.657 vs. 0.248, $p < 0.001$). Hospital type, age, and moderate and severe comorbid conditions were also slightly associated with the patient compliance score (0.044 vs. 0.016 vs. 0.028 vs. 0.039, $p < 0.001$, respectively) (Table 4).

Discussion

We conducted this study to evaluate compliance with the Tokyo Guidelines for the management of acute cholangitis, based on the database associated with the DPC system. In this study, we found that compliance with the Tokyo Guidelines became higher in relation to the severity of acute cholangitis. Compared with mild or moderate cases, intensive care such as systemic antibiotics and supportive care is more imperative when treating severe acute cholangitis [7–9, 11]. In addition, severe cases are more likely to result in serious conditions such as septic shock, mental symptoms, and metabolic acidosis [21, 22]; indeed, these conditions are associated with poor prognosis and high mortality [21, 22]. Therefore, clinicians are more likely to follow the recommendations in the Tokyo Guidelines for the treatment of acute cholangitis when the condition is severe.

On the contrary, in patients with mild acute cholangitis, there was considerably poor compliance with the Tokyo Guidelines. The cause of this poor compliance seemed to be mainly related to antimicrobial therapy. Especially, significantly lower compliance (compared with that in severe cases) in the use of intravenous antimicrobial therapy and the use of the recommended intravenous antimicrobial drugs was observed in the present study. We confirmed that most of the patients with mild acute cholangitis in the data of the Japanese administrative database had received oral antimicrobial therapy (data not presented). Regrettably, the Tokyo Guidelines have not described recommended oral antimicrobial drugs [12]. Lipsett and Pitt [1] reported that patients with mild acute cholangitis may be treated with oral antimicrobial drugs. Therefore, we think that the Tokyo Guidelines should show recommended oral antimicrobial drugs for patients with mild acute cholangitis. Regarding the use of recommended intravenous antimicrobial drugs, the SBT/CPZ has not been recommended for patients with mild acute cholangitis in the Tokyo Guidelines [12]. Nevertheless, SBT/CPZ was the most used drugs for mild acute cholangitis in the present study. This result suggests that some clinicians had used the antimicrobial drugs empirically without reference to the Tokyo Guidelines. The Tokyo Guidelines recommend that the empirical administration of antimicrobial drugs should be avoided [12]. Therefore, the dissemination of more information about the appropriate use of drugs may be required for better compliance with the recommendations for antimicrobial therapy in patients with mild acute cholangitis.

Of note, in the present study, the frequency of cholecystectomy after the resolution of cholangitis was significantly higher in patients with mild cases than in patients with moderate or severe cases. We think that this

Table 3 Compliance with recommendations according to severity criteria (%)

Grades of acute cholangitis	Grade I (mild)	Grade II (moderate)	Grade III (severe)	*p* value
(1) Intravenous antimicrobial therapy	20.8	92.9	98.8	<0.001
(2) Use of recommended antimicrobial drugs according to severity[a]	45.8	98.4	98.9	<0.001
(3) Use of antimicrobial drugs with good biliary penetration[b]	90.4	95.4	90.3	<0.001
(4), (5) Compliance with recommended duration of antimicrobial therapy[c]	81.0	92.3	98.2	<0.001
(6) Endoscopic biliary drainage	0	75.8	94.1	<0.001
(7) Immediate biliary drainage (within 2 days)	0	36.7	52.4	<0.001
(8) Bile cultures at all available opportunities	0	36.8	49.2	<0.001
(9) Blood cultures at all available opportunities	11.2	34.2	79.3	<0.001
(10) Cholecystectomy after the resolution of cholangitis	40.2	30.7	12.1	<0.001

All *p* values were derived from the χ^2 test

[a] Kinds of recommended antimicrobial drugs for each grade described in the Tokyo guidelines (grade I: cefazoline, cefmetazole, cefotiam, oxacephem, flomoxef, ampicillin/sulbactam; grades II and III: ampicillin/sulbactam, piperacillin/tazobactam, sulbactam/cefoperazone, ceftriaxone, ceftazidime, cefepime, cefozopran, aztreonam, ciprofloxacin, levofloxacin, pazufloxacin, meropenem, imipenem/cilastatin, doripenem)

[b] Kinds of antimicrobial drugs with good biliary penetration also described in the Tokyo guidelines (piperacillin, aspoxicillin, piperacillin/tazobactam, ampicillin, cefazoline, cefmetazole, cefotiam, flomoxef, sulbactam/cefoperazone, ceftriaxone, cefozopran, cefpirome, ceftazidime, cefoperazone, ciprofloxacin, pazufloxacin, aztreonam, and clindamycin)

[c] The recommended duration of antimicrobial therapy in grade I was defined as within 3 days, whereas that in grades II or III was defined as beyond 5 days

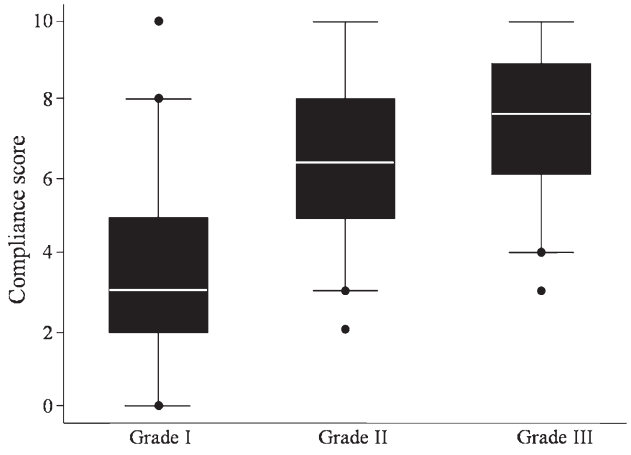

Fig. 2 Patient compliance scores according to severity of acute cholangitis

discrepancy is a reflection of a patient's condition during hospitalization. In our study, the patients with severe cases included a higher proportion of those with chronic comorbid conditions, as shown in Table 2. Many studies have reported that cholecystectomy, especially via laparoscopic procedures, is safe and effective for patients with gallstone diseases [23–25]. However, complication rates and mortality were significantly higher in patients with severe cases of the disease [25, 26]. Giger et al. [26] reported that a higher proportion of postoperative systemic complications of laparoscopic cholecystectomy had been encountered in cases with a higher American Society of Anesthesiologists (ASA) score. Therefore, many surgeons may consider that cholecystectomy after the resolution of cholangitis should depend on a patient's condition during hospitalization. To solve this discrepancy, further clinical trials involving cholecystectomy in accordance with the severity of acute cholangitis are needed.

The greatest strength of the present study is its use of individual data. One of the advantages of using the administrative database associated with the DPC system was that it allowed for the evaluation of a large number of acute-care hospitals; as a result, our investigation involved a nationally representative sample of patients in a community setting [27, 28]. In addition, medical data, such as procedures, drugs, and devices have been coded with the Japanese original payment codes for the DPC reimbursement system [27, 28]. These data have been recorded for each patient on a daily basis [27, 28]. Therefore, this administrative database enabled a detailed evaluation of compliance with the Tokyo Guidelines based on individual medical treatments.

Several limitations of this study should be mentioned. First, we did not consider the analyses of outpatients. In mild cases of acute cholangitis, outpatients are sometimes treated with antimicrobial therapy alone [1, 2]. Therefore, there is a possibility that the number of patients with mild acute cholangitis has been underestimated. However, blood culture and cholecystectomy (other recommendations for mild acute cholangitis) are usually performed during hospitalization. Second, we could not evaluate compliance with antimicrobial drug use for patients with renal failure (recommendation of drug dosage adjustment for antimicrobial therapy in patients with decreased renal function (recommendation A) [12]). The Tokyo Guidelines

Table 4 Linear regression analysis of factors associated with patient compliance

Independent variables	Unstandardized coefficient	95% Confidence interval	Standardized coefficient	*p* value
Intercept	3.103	[3.038, 3.169]		<0.001
Reference: grade I (mild)				
Grade II (moderate)	3.629	[3.596, 3.660]	0.248	<0.001
Grade III (severe)	4.630	[4.523, 4.738]	0.657	<0.001
Reference: community hospital				
Academic hospitals	0.182	[0.158, 0.206]	0.044	<0.001
Age	0.066	[0.025, 0.104]	0.016	<0.001
Male	0.009	[−0.027, 0.045]	0.001	0.528
Ambulance	0.017	[−0.023, 0.058]	0.002	0.402
Reference: CCI of 0 (mild)				
1 (moderate)	0.179	[0.126, 0.232]	0.028	<0.001
2 or more (severe)	0.215	[0.175, 0.256]	0.039	<0.001

CCI Charlson comorbidity index

F test for the model; $p < 0.001$, $R^2 = 0.047$

recommend that renal function should be estimated by laboratory data, such as serum creatinine clearance, and the drug dosage changed in accordance with patients' renal function [12]. In the DPC system, laboratory data or image findings have not been represented [27, 28]. However, the DPC system enables the follow-up survey of drug use, as shown in Fig. 1. In a previous study, Matsuda et al. [28] reported that the administrative database associated with the DPC system was very useful for the evaluation of chemotherapy drugs for lung cancer in DPC participating hospitals. We think that the DPC database provides good information regarding the use of antimicrobial drugs in patients with decreased renal function, and that there is the possibility of reconsidering and revising the guidelines for antimicrobial therapy.

In conclusion, we used the administrative database associated with the DPC system to report the present circumstances regarding compliance with the Tokyo Guidelines for acute cholangitis. We demonstrated that compliance with the Tokyo Guidelines for acute cholangitis became higher with the severity of acute cholangitis. We hope that this study will assist in further improvement and reconsideration of the Tokyo Guidelines for acute cholangitis.

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An Observational Study Using a National Administrative Database to Determine the Impact of Hospital Volume on Compliance With Clinical Practice Guidelines

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Background: Little information is available on the relationship between hospital volume and compliance with clinical practice guidelines (CPGs).

Objectives: To investigate the relationship between hospital volume and compliance with CPGs using a Japanese administrative database.

Design and Subjects: This was an observational study that included 60,842 patients with acute cholangitis from 829 hospitals in Japan.

Measures: Hospital volume was categorized into the following 3 groups based on the number of cases of acute cholangitis during the study period: low-volume hospitals (LVHs; n = 20,869), medium-volume hospitals (MVHs; n = 18,387), and high-volume hospitals (HVHs; n = 21,586). We further collected patient data with regard to CPGs for acute cholangitis, and counted the number of recommendations that had been complied with for each patient. CPGs compliance score was defined as the rate of compliance with these recommendations for each patient (range, 0–10). Aggregated CPGs compliance score was measured according to hospital volume.

Results: Mean CPGs compliance score in HVHs was significantly higher than that in MVHs and LVHs (6.8 ± 1.6 vs. 5.6 ± 1.5 vs. 3.9 ± 1.4, respectively; $P < 0.001$). Multiple linear regression analysis revealed that hospital volume was most significantly associated with CPGs compliance score. The standardized coefficient for CPGs compliance score in HVHs was 0.689, whereas that of MVHs was 0.366 ($P < 0.001$).

Conclusions: This study demonstrated that hospital volume was significantly associated with compliance with CPGs and that the Japanese administrative database was a viable tool for the monitoring of compliance with CPGs.

Key Words: clinical practice guidelines, compliance, hospital volume, administrative database

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Clinical practice guidelines (CPGs) have increasingly become a familiar part of clinical practice over the last 2 decades, and are of interest worldwide.[1,2] CPGs have proliferated in various areas of medicine and continue to be promoted as a means of improving the quality of patient care and patient health outcomes, reducing practice variation, and promoting more efficient use of health resources.[3,4] As defined by the Institute of Medicine, CPGs are systematically developed statements to assist practitioner and patient decision making about appropriate health care for specific clinical circumstances.[1–3] CPGs offer concise instructions on which diagnostic or screening tests to order, how to provide medical or surgical services, how long patients should stay in hospital, and further clinical practice details.[1] Therefore, many clinicians look to CPGs for credible assistance in resolving problems in daily practice.[5,6]

There have been many previous studies into the relationship between patient outcome and compliance with CPGs.[7–10] Quaglini et al[7] reported that guideline compliance was a significant independent indicator of medical cost and length of hospital stay (LOS) in patients with stroke. Other studies have also reported that adherence to CPGs improves the health outcome of patients in terms of in-hospital mortality or LOS.[8–10] These results suggest that CPGs that are well followed are substantially beneficial for patients.

However, little information is available on the relationship between hospital volume and compliance with CPGs on account of patient-based data. In addition, there have been no studies where an administrative database has been used to quantify compliance with CPGs throughout the process of care in community-based facilities. If a relationship between compliance with CPGs and hospital volume, as well as clinical outcome, could be demonstrated, then this type of

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study could be used as part of a quality improvement initiative aimed at attempting to steer patients toward hospitals that are more compliant with CPGs, thereby allowing improvement of care.

In this study, we investigated the relationship between hospital volume and compliance with CPGs. This was achieved using the national administrative database developed in a Japanese case-mix system project named Diagnosis Procedure Combination (DPC). Factors explaining the variation of compliance were also determined.

METHODS

The DPC System and Database

In 2003, Japanese case-mix projects based on the DPC system were introduced to 82 academic hospitals (80 university hospitals, the National Cancer Centre, and the National Cardiovascular Centre).[11–15] Insurance reimbursement using the DPC system is quite prevalent in Japan, and the administrative database of the DPC system has increased the representation of acute care hospitals. As of 2007, data from approximately 450,000 inpatients have been compiled, which represents approximately 90% of all acute care inpatient hospitalizations.[12]

The administrative database of the DPC system includes each patient's discharge summary and claim information, including principal diagnosis, comorbidities, and complications during hospitalization. These data are coded in the International Classification of Diseases and Injuries-10th. In addition, this administrative database also contains detailed medical information, such as all surgical procedures, medications, and devices that has been indexed in the original Japanese code. These codes are determined by the Ministry of Health, Labor and Welfare of Japan. The administrative database also includes the quantity and date of all care delivered on a daily basis.[11,12]

Selected CPGs and Recommendations

We selected CPGs for acute cholangitis as an example for this study. CPGs for acute cholangitis were posted in the *Journal of Hepato-Biliary-Pancreatic Surgery* in 2007.[16–21] These CPGs are the world's first international guidelines for the clinical management of acute cholangitis. These guidelines are strongly expected to be broadly used in medical practice for acute cholangitis throughout the world and have been awaiting evaluation.[21]

Selected recommendations for acute cholangitis are shown in Table 1. Ten recommendations were given (7 items of recommendation A [based on good available evidence] and 3 items of recommendation B [based on moderate available evidence]).[18,19] These grades of recommendation are based on the Kish method of classification.[16]

Severity of Acute Cholangitis

Some recommendations for acute cholangitis have been represented according to severity criteria (Table 1). CPGs described that severity of acute cholangitis should be divided into 3 grades.[21] The severity of acute cholangitis is defined as follows: grade I (mild acute cholangitis that responds to initial medical treatment, such as hydration or antimicrobial therapy), grade II (moderate acute cholangitis that does not respond to initial medical treatment and requires biliary drainage), and grade III (acute cholangitis that requires initial medical treatment, biliary drainage, and organ support). These grades are the original classification criteria as described by the organizing committee of CPGs for acute cholangitis.[21] This committee has emphasized that the Acute Physiology and Chronic Health Evaluation II system or Marshall's system should not be used because these systems have not been satisfactorily validated in patients with acute cholangitis.[21]

TABLE 1. Selected Recommendations in the Clinical Practice Guidelines (CPGs) for Acute Cholangitis

Recommendation A
(1) Intravenous antimicrobial therapy
(2) Use of antimicrobial drugs according to the severity of acute cholangitis
(3) Use of antimicrobial drugs with good biliary penetration
(4) Maximum 3 d of administration of antimicrobial drugs for patients with mild (grade I) acute cholangitis
(5) Minimum 5 d of administration of antimicrobial drugs for patients with moderate (grade II) or severe (grade III) acute cholangitis
(6) Endoscopic biliary drainage
(7) Immediate biliary drainage
Recommendation B
(8) Bile culture
(9) Blood culture
(10) Cholecystectomy

In this study, we equated grade I with acute cholangitis that required hydration or intravenous or oral antimicrobial therapy, either alone or in combination. Grade II was identified as acute cholangitis that required either endoscopic biliary drainage (EBD) or percutaneous transhepatic cholangial drainage (PTCD) associated with treatment for grade I. Grade III was identified as critically ill patients with acute cholangitis who required either ventilation or hemodiafiltration associated with treatment for grade II. These classifications were confirmed for every patient using the administrative database, and not by self-report.

Study Setting

Between April and December 2008, 61,188 patients with acute cholangitis in 829 DPC participating hospitals (82 academic and 747 community hospitals) were selected. These hospitals are scattered throughout Japan and play a leading role in providing acute care medicine, advancing medical research, and educating students and residents.[13,14] The principal diagnosis of acute cholangitis, defined as code K830, was recorded using International Classification of Diseases and Injuries-10th code. For this analysis, we excluded 346 patients aged 15 years and less as the causes of pediatric acute biliary tract infections are quite different from those of adult acute biliary tract infection (eg, congenital biliary atresia or dilatation, post liver transplantation or pancreaticobiliary maljunction).[20]

TABLE 2. Clinical Characteristics and Presentations of Patients Sorted by Hospital Volume

Volume Category	Low Volume	Medium Volume	High Volume	*P*
No. patients (hospitals)	20,869 (499)	18,387 (188)	21,586 (142)	
Hospital type (%)				<0.001*
Academic hospitals	5.6	17.6	14.8	
Community hospitals	94.4	82.4	85.2	
No. patients (%)				<0.001*
Grade I	85.1	80.1	79.5	
Grade II	14.5	19.4	19.9	
Grade III	0.4	0.5	0.6	
Mean age—yr, (SD)	68.6 (15.6)	68.0 (15.3)	67.0 (15.2)	<0.001†
Elderly patients (%)	35.1	37.2	37.9	<0.001*
Male patients (%)	55.0	53.4	52.9	<0.001*
Use of ambulance (%)	10.0	10.7	9.4	<0.001*
Use of intensive care unit (%)	2.4	2.0	2.8	<0.001*
Mean CCI—score, (SD)	1.4 (1.8)	1.3 (1.8)	1.6 (2.2)	<0.001‡
Mean length of stay—d, (SD)	18.3 (18.0)	16.6 (16.2)	15.1 (14.8)	<0.001‡
In-hospital mortality (%)	2.8	2.8	2.5	0.041*

*P values were derived from the χ^2 test.
†P value was derived from one-way factorial analysis of variance (ANOVA).
‡P values were derived from the Kruskal-Wallis test.
SD indicates standard deviation; CCI, Charlson comorbidity index.

The research protocol of the study was approved by the ethics committee of medical care and research of the University of Occupational and Environmental Health, Kitakyushu, Japan.

Study Variables

Age, gender, hospital type, chronic comorbid conditions, use of ambulance and intensive care unit (ICU), LOS, in-hospital mortality, frequency of intravenous antimicrobial therapy, kinds of antimicrobial drugs, duration of administration of antimicrobial drugs, EBD, PTCD, bile and blood culture, and cholecystectomy were some of the variables analyzed in this study. These variables were defined according to published guidelines and literature.[17,22,23] Because elderly patients (defined as patients aged 75 years or older in these CPGs) had a higher risk for biliary drainage or surgical procedures as compared with younger patients, patients were sorted into the following 2 groups: under 75 years and 75 years or older.[19] In this study, hospital type was classified as either academic or community hospital.[13–15] To assess the severity of chronic comorbid conditions, we used the Charlson Comorbidity Index (CCI), which has been most widely used for recording comorbidity and was validated in various studies.[24,25] CCI score was calculated for each patient as in previous studies.[24,26] Immediate biliary drainage was defined as the drainage (either EBD or PTCD) that had been performed within 2 days after admission, as described in previous studies.[19,27]

Hospital volume was expressed as the number of cases during the study period and was initially evaluated as a continuous variable. However, the following categorical variables defining 3 categories of hospital volume were created to simplify the presentation of the results: low-volume hospitals (LVHs) had less than 80 cases, medium-volume hospitals (MVHs) had 80 to 120 cases, and high-volume hospitals (HVHs) had more than 120 cases during the study period. These categories were based on cut-off values that yielded roughly equivalent numbers of patients in each volume category.[28] This method has frequently been used in previous studies of hospital volume.[28–30]

Main Outcomes

The number of the recommendations that had been accomplished for every patient were counted. The compliance rate of the recommendations in grade I was calculated for 6 recommendations—item (1) to (4) and (9), (10)—as shown in Table 1, while that of the recommendations in grade II and III were calculated for 9 recommendations—item (1) to (3) and (5) to (10)—as shown in Table 1. In this study, CPGs compliance score was defined as the compliance rate of recommendations for every patient (where "0" represents 0% compliance and "10" represents 100% compliance with recommendations). The calculated score was rounded off to the nearest integer.

Statistical Analysis

For tests of statistical significance, we used the χ^2 test for categorical data, and 1-way factorial analysis of variance and the Kruskal-Wallis tests for continuous variables. CPGs compliance was evaluated according to the 3 categories of hospital volume using CPGs compliance score.

It is not clear whether compliance with these CPGs improves patient outcomes. We therefore investigated the relationship between compliance with CPGs and in-hospital mortality as a clinical outcome, using multiple logistic regression models. Patients were defined as high- or low-compliance, where high-compliance patients were patients with a greater than mean compliance score in each grade. We

TABLE 3. Compliance With Recommendations and Mean Compliance Score Sorted by Hospital Volume

Volume Category	Low Volume	Medium Volume	High Volume	*P*
Compliance with recommendations (%)				
Grade I				
(1) Intravenous antimicrobial therapy	9.4	16.2	36.0	<0.001*
(2) Use of antimicrobial drugs recommended in grade I†	72.6	89.2	98.9	<0.001*
(3) Use of antimicrobial drugs with good biliary penetration‡	76.4	95.7	97.1	<0.001*
(4) Administration of antimicrobial drugs within 3 d	71.2	83.2	89.1	<0.001*
(9) Blood culture	7.6	9.1	16.7	<0.001*
(10) Cholecystectomy	17.9	40.7	62.9	<0.001*
Grade II				
(1) Intravenous antimicrobial therapy	88.6	91.1	97.7	<0.001*
(2) Use of antimicrobial drugs recommended in grade II†	97.0	98.5	99.5	<0.001*
(3) Use of antimicrobial drugs with good biliary penetration‡	93.2	95.4	97.5	<0.001*
(5) Administration of antimicrobial drugs beyond 5 d	89.5	92.3	95.2	<0.001*
(6) Endoscopic biliary drainage	58.8	73.3	92.6	<0.001*
(7) Immediate biliary drainage	22.5	37.0	42.7	<0.001*
(8) Bile culture	13.8	26.8	63.8	<0.001*
(9) Blood culture	21.1	29.4	53.5	<0.001*
(10) Cholecystectomy	13.1	22.4	46.7	<0.001*
Grade III				
(1) Intravenous antimicrobial therapy	97.6	97.9	98.3	0.909*
(2) Use of antimicrobial drugs recommended in grade III†	97.6	95.9	97.5	0.731*
(3) Use of antimicrobial drugs with good biliary penetration‡	96.3	94.8	96.7	0.779*
(5) Administration of antimicrobial drugs beyond 5 d	95.1	93.8	96.7	0.748*
(6) Endoscopic biliary drainage	76.8	83.5	91.7	0.013*
(7) Immediate biliary drainage	40.2	60.8	65.0	0.001*
(8) Bile culture	36.6	58.8	63.3	0.002*
(9) Blood culture	48.8	66.7	69.0	0.011*
(10) Cholecystectomy	7.3	11.3	23.3	0.003*
Mean compliance score (SD)				
Grade I	3.8 (1.2)	5.4 (1.5)	6.6 (1.6)	<0.001§
Grade II	5.3 (1.6)	6.4 (1.5)	7.7 (1.4)	<0.001§
Grade III	6.8 (1.4)	7.5 (1.3)	7.9 (1.4)	0.014§
All patients	3.9 (1.4)	5.6 (1.5)	6.8 (1.6)	<0.001§

*P values were derived from the χ^2 test.

†Recommended antimicrobial drugs for each grade were previously described in the clinical practice guidelines (CPGs) (Grade I: cefazolin, cefmetazole, cefotiam, oxacephem, flomoxef, ampicillin/sulbactam; Grade II and III: ampicillin/sulbactam, piperacillin/tazobactam, sulbactam/cefoperazone, ceftriaxone, ceftazidime, cefepime, cefozopran, aztreonam, ciprofloxacin, levofloxacin, pazufloxacin, meropenem, imipenem/cilastatin, doripenem).

‡Antimicrobial drugs with good biliary penetration were previously described in the CPGs (piperacillin, aspoxicillin, piperacillin/tazobactam, ampicillin, cefazolin, cefmetazole, cefotiam, flomoxef, sulbactam/cefoperazone, ceftriaxone, cefozopran, cefpirome, ceftazidime, cefoperazone, ciprofloxacin, pazufloxacin, aztreonam and clindamycin).

§*P* values were derived from one-way factorial analysis of variance (ANOVA).

SD indicates standard deviation.

addressed potentially confounding variables in the case-mix data by accounting for the presence of chronic comorbid conditions and additional variables related to in-hospital mortality and CPGs compliance score, such as CCI, hospital type, age, gender, and use of ambulance and ICU. Robust standard errors were also used to allow for the effect of clustering of patients within hospitals.

We used multiple linear regression models to identify the effect of hospital volume on CPGs compliance score. In addition, we defined hospital compliance with CPGs as the percentage of high-compliance patients per hospital, as defined in previous studies.[31,32] Simple linear regression analysis was conducted to determine the correlation between hospital compliance with CPGs and hospital volume. This correlation was evaluated separately for academic and community hospitals.

A value of $P < 0.05$ was considered significant. All statistical analysis was performed using the STATA statistical software package version 9.0 (Stata Corporation, College Station, TX).

RESULTS

We identified a total of 60,842 patients across 829 hospitals for this study. Academic hospitals comprised 5.6% of LVHs, 17.6% of MVHs, and 14.8% of HVHs. The proportion of elderly patients was highest in HVHs, whereas that of male patients was highest in LVHs. Use of ambulance and ICU differed significantly between hospitals with different volumes. Significant variations in mean LOS were also observed between hospital volume categories. Lower mor-

tality was observed in HVHs than in LVHs and MVHs (2.5% vs. 2.8% vs. 2.8%, respectively). Significant differences between hospital volume categories existed for a number of independent variables (Table 2).

The recommendations of CPGs for grade I and II patients were complied with more in HVHs than in LVHs and MVHs. There were no significant differences among the hospitals in terms of use of antimicrobial therapy in grade III patients. However, EBD, immediate biliary drainage, bile and blood culture, and cholecystectomy were significantly higher in HVHs than in LVHs and MVHs. All the mean CPGs compliance scores differed significantly among the different hospital volume categories for grade I and II patients. For grade III patients, the highest mean CPGs compliance score was found in HVHs (7.9 ± 1.4 in HVHs vs. 7.5 ± 1.3 in MVHs vs. 6.8 ± 1.4 in LVHs, $P = 0.014$). As part of the sensitivity analyses, hospitals were grouped by tercile in terms of their CPGs compliance scores. The distribution of scores was evaluated by comparing scores between the terciles for each hospital grade. The statistical significances were similar between the top and bottom tercile (data not presented). Overall, the mean CPGs compliance score was significantly higher in HVHs compared with MVHs and LVHs (6.8 ± 1.6 vs. 5.6 ± 1.5 vs. 3.9 ± 1.4, respectively, $P < 0.001$; Table 3).

With regard to in-hospital mortality, multiple logistic regression analysis demonstrated a significant decrease in in-hospital mortality in high-compliance patients, compared with low-compliance patients. The odds ratio for high-compliance patients was 0.856 (95% confidence interval, 0.77–0.952; $P = 0.004$). This result demonstrated that the CPGs used in this study significantly contributed to outcome in patients with acute cholangitis. Elderly and male patients, use of ambulance and ICU, and comorbid conditions were also associated with increased risks of in-hospital mortality (Table 4).

After adjusting for potential confounding effects of demographic and clinical variables, hospital volume was the most significant factor among all variables in predicting CPGs compliance. The standardized coefficient of HVHs was 0.689, whereas that of MVHs was 0.366 for CPGs compliance. The standardized coefficient of hospital type, gender, and use of ambulance and ICU showed minor association with CPGs compliance in this study (Table 5).

Figure 1 shows the relationship between hospital compliance with CPGs and hospital volume. Simple regression analysis revealed significant positive correlations between hospital compliance and hospital volume for both academic and community hospitals ($R^2 = 0.458$ and 0.420, $P < 0.001$, respectively).

TABLE 4. Logistic Regression Analysis of Factors Associated With In-Hospital Mortality

Independent Variables	Odds Ratio	95% Confidence Interval	*P*
Compliance with CPGs			
Low-compliance patients	1.000 (reference)		
High-compliance patients	0.856	0.770–0.952	0.004
Hospital type			
Community	1.000 (reference)		
Academic	1.062	0.962–1.173	0.234
Age			
Younger than 75 yr	1.000 (reference)		
75 yr or older	2.847	2.567–3.157	<0.001
Sex			
Female	1.000 (reference)		
Male	1.235	1.117–1.365	<0.001
Ambulance			
Not used	1.000 (reference)		
Used	1.835	1.615–2.084	<0.001
Intensive care unit			
Not used	1.000 (reference)		
Used	1.580	1.221–2.044	0.001
Charlson Comorbidity Index			
0	1.000 (reference)		
1 or more	1.119	1.008–1.244	0.035

Hosmer-Lemeshow goodness for fit; $P = 0.415$.
CPG indicates clinical practice guidelines.

DISCUSSION

We conducted this study to investigate the relationship between hospital volume and compliance with CPGs throughout the process of patient care. We also used the Japanese administrative database of the DPC system to determine factors leading to the variation in compliance with the CPGs. These studies revealed that hospital volume was significantly associated with compliance with CPGs.

Although many reports have focused on the relationship between patient outcome and compliance with CPGs, studies on the relationship between hospital volume and compliance are rare. To our knowledge, a report describing the relationship between hospital volume and compliance with CPGs has been published. Williams et al[33] studied the relationship between hospital volume and CPGs compliance in the treatment of acute myocardial infarction and heart failure in 3000 hospitals in the United States, and evaluated compliance with every recommendation. This report relied on volume cut-points to create hospital volume groups, and concluded that hospitals with larger case volumes were significantly more likely to apply CPGs than those with smaller case volumes. However, compliance with CPGs for overall medical treatment should be comprehensively evaluated when developing efficient quality improvement initiatives and implementing health policy. Even though this observation was made, Williams et al did discuss the need for independent assessment of individual processes.[33] In addition, this study relied on hospital self-reported performance data, which could be a source of bias.[33] By contrast, the use of a national administrative database enables the potential bias to be minimized. Tsai et al[34] reported that a national administrative database was useful for avoiding potential bias that may occur in hospitals with a specialty interest in bariatric surgery. The present study is the first report to demonstrate a relationship between hospital volume and

TABLE 5. Linear Regression Analysis of Factors Associated With CPGs Compliance Score

Independent Variables	Unstandardized Coefficient	95% Confidence Interval	Standardized Coefficient	*P*
Intercept	3.946	3.917 to 3.975	<0.001	
Reference: low-volume hospitals				
Large-volume hospitals	2.758	2.729 to 2.787	0.689	<0.001
Medium-volume hospitals	1.527	1.496 to 1.557	0.366	<0.001
Reference: community hospital				
Academic hospitals	0.067	0.042 to 0.091	0.015	<0.001
75 yr of age or older	0.024	−0.017 to 0.064	0.003	0.257
Male	0.056	0.032 to 0.081	0.015	<0.001
Use of ambulance	0.157	0.131 to 0.182	0.039	<0.001
Use of intensive care unit	0.122	0.049 to 0.195	0.023	<0.001
Charlson Comorbidity Index	0.003	−0.003 to 0.009	0.003	0.317

F-test for the model; $P < 0.001$, $R^2 = 0.466$.
CPG indicates clinical practice guidelines.

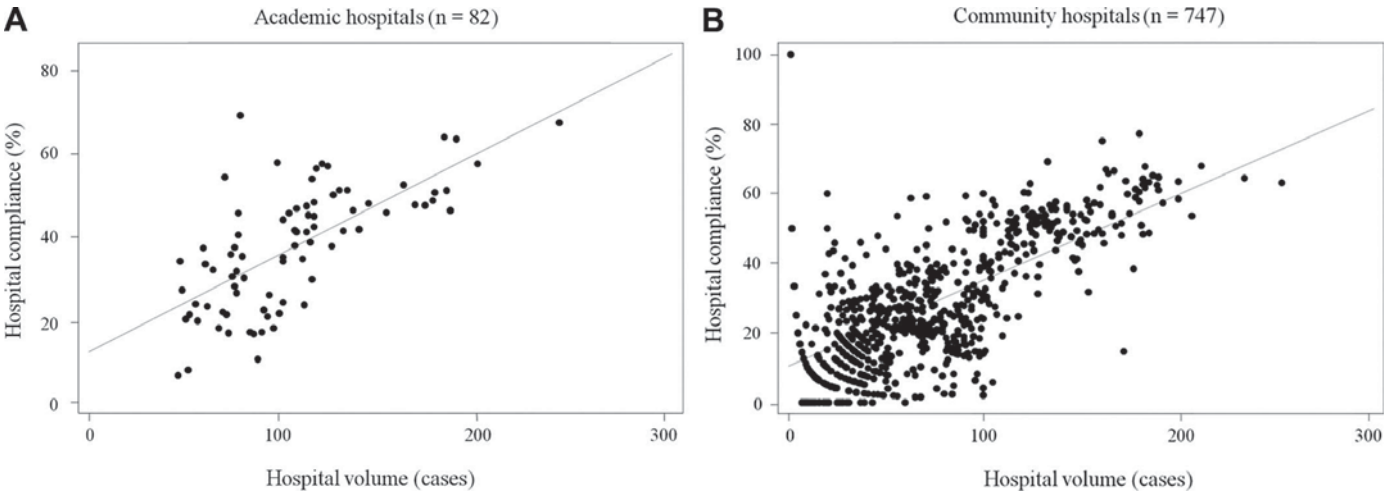

FIGURE 1. Simple linear regression analysis of hospital compliance with CPGs versus hospital volume. The regression equations are as follows: $y = 0.240\ x + 12.206$ ($R^2 = 0.458$, $P < 0.001$) for academic hospitals (A) and $y = 0.247\ x + 10.536$ ($R^2 = 0.420$, $P < 0.001$) for community hospitals (B).

CPGs compliance throughout the process of patient care using a national administrative database.

This study identified a significant association between hospital volume and CPGs compliance. This difference in compliance among hospitals with different patient volumes appeared to be mainly accounted for by specific procedures; compliance with recommendations regarding specific procedures or treatments such as biliary drainage, bile and blood culture, and cholecystectomy was significantly higher in hospitals with larger case volumes for all grades of acute cholangitis. These results are likely to be related to the structural characteristics of hospitals, such as available facilities and resources or presence of specialists. Many previous reports have shown a significant association between hospital volume and patient outcome for a wide variety of surgical procedures and medical conditions, and have indicated that hospitals with larger case volumes have greater resources or treatment facilities.[29–31,35,36] It is therefore plausible that hospitals with larger case volumes are more able to comply with CPGs with regard to specific procedures. In addition, some previous studies reported that hospitals with large case volumes were more likely to have specialists and specialized teams who are able to provide multidisciplinary care, which significantly contributed to improved clinical outcomes.[37,38] In a recent study, Hollowell et al[39] reported that specialists more consistently met CPGs regarding breast cancer treatments. Therefore, features of the hospital itself for specific procedures may be associated with the observed increase in CPGs compliance at higher volume hospitals.

The use of clinical data represents a major strength of the current study. According to a survey of National Medical Care Insurance Services in Japan in 2008, significantly more procedures and treatments for acute cholangitis were performed in acute care than in nonacute hospitals,[40] and the DPC administrative database evaluated a large number of such acute care hospitals.[11,12] The data from this administrative database therefore closely reflect the clinical circumstances of the procedures and treatments for acute cholangitis. In addition, detailed medical data such as all procedures, medications, and devices have been exhaustively coded with Japa-

nese original payment codes.[11,12] These data have been recorded on a daily basis for each patient.[11,12] Therefore, this administrative database would also enable interested parties to measure CPGs compliance with individual detailed medical treatments.

A limitation of this study was that laboratory test data for patients with renal insufficiency could not be evaluated. The CPGs recommend the estimation of serum creatinine clearance and the management of drug dosage in accordance with presenting renal function,[18] but laboratory data and imaging findings were not recorded in the Japanese administrative database.[11,12] However, the database does include follow-up drug use information,[12] and we therefore believe that use of this database remains valuable, as several CPGs do not indicate the appropriate drug dosage, but merely highlight the importance of administering a relevant medication.

Despite these limitations, the current findings have implications for health care policy decision-making and the quality of patient care. First, health policy in Japan has been based on free access to hospitals with no gate keeping, unlike many European countries or the United States.[11,12] Therefore, the centralization or distribution of patients associated with the policy of concentrating or allocating medical services to reduce local access does not occur in Japan.[11,12] However, the current findings provide good evidence supporting centralization or distribution of patients. Further research examining the association between hospital volume and compliance with various CPGs might contribute to the patient referral policy in various areas of medical treatment in Japan. Second, clinical governance has been recently introduced as a systematic approach to maintaining and improving the quality of patient care in the health care system.[41] There is no doubt that the monitoring of CPGs compliance is a useful evidence for maintaining and improving quality of medical care as a measure of quality improvement.[7–10] As this study demonstrated, some hospitals had poor compliance with CPGs (Fig. 1). The use of the Japanese administrative database enabled the identification of the hospitals with insufficient adherence to CPGs to occur. According to a recent report describing the Quality Counts program run by the Employer Health Care Alliance Cooperative, hospitals with public-reporting programs had engaged more in quality-improvement activities.[42] Therefore, monitoring of compliance level to CPGs based on the administrative database may be a promising policy implementation allowing the accountability of clinical practice or the improvement of the quality of medical care. In addition, research refining or validating CPGs through the measurement of the effect of patient mix on the variation of CPGs compliance, in conjunction with the adjustment of time trend effects, should be conducted in the future.

In conclusion, we demonstrated that hospital volume was significantly associated with compliance with CPGs. In addition, the Japanese administrative database was a feasible tool for the monitoring of compliance with CPGs. The current findings could contribute to the formation of health policy, for example by encouraging centralization or steering patients toward hospitals that are more compliant with CPGs. Quality improvement initiatives could also focus on monitoring and improving CPG compliance. To enhance the feasibility of CPGs to relevant case-mixes, further studies to identify the contribution that patient mix imposes on the variation in compliance with CPGs are required.

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【3-4　クリニカルクエスチョンの設定】CQ4

スコープで取り上げた重要臨床課題（Key Clinical Issue）
抗菌薬と胆管ドレナージ以外の重症胆管炎に対する有効な治療

CQの構成要素	
P （Patients, Problem, Population）	
性別	指定なし
年齢	指定なし
疾患・病態	重症急性胆管炎
地理的要件	日本
その他	なし

I （Interventions）／C （Comparisons, Controls）のリスト
トロンボモジュリン使用有/トロンボモジュリン使用無

O （Outcomes）のリスト

	Outcomeの内容	益か害か	重要度	採用可否
O1	Mortality	害	点	○
O2	DIC離脱率	益	点	○
O3			点	
O4			点	
O5			点	
O6			点	
O7			点	
O8			点	
O9			点	
O10			点	

作成したCQ

【4-6 評価シート 観察研究】CQ4

診療ガイドライン	急性胆管炎
対象	DICを伴う急性胆管炎
介入	トロンボモジュリン投与
対照	トロンボモジュリン非投与

*バイアスリスク、非直接性
　各ドメインの評価は"高(-2)"、"中/疑い(-1)"、"低(0)"の3段階
　まとめは"高(-2)"、"中(-1)"、"低(0)"の3段階でエビデンス総体に反映させる
** 上昇要因
　各項目の評価は"高(+2)"、"中(+1)"、"低(0)"の3段階
　まとめは"高(+2)"、"中(+1)"、"低(0)"の3段階でエビデンス総体に反映させる
各アウトカムごとに別紙にまとめる

アウトカム	Mortality

個別研究		バイアスリスク*							上昇要因**				非直接性*					リスク人数(アウトカム率)								
		選択バイアス	実行バイアス	検出バイアス	症例現象バイアス	その他																				
研究コード	研究デザイン	背景因子の差	ケアの差	不適切なアウトカム測定	不完全なフォローアップ	不十分な交絡の調整	その他のバイアス	まとめ	量反応関係	効果減弱交絡	効果の大きさ	まとめ	対象	介入	対照	アウトカム	まとめ	対照群分母	対照群分子	(%)	介入群分母	介入群分子	(%)	効果指標(種類)	効果指標(値)	信頼区間
Suetani	症例集積	-2	0	0	0	0	0	-2	0	0	0	0	0	0	0	0	0	36	10	27.8	30	4	13.3	N/A	N/A	N/A
Nakahara	症例集積	-2	-1	-2	0	0	0	-2	0	0	0	0	0	0	0	0	0	6	N/A	N/A	8	N/A	N/A	N/A	N/A	N/A

コメント(該当するセルに記入)

	抗DIC薬と抗菌薬に有意																									
	検定されていない。	他の抗DIC薬使用に	群別のmortalityが不明																							

【4-6 評価シート 観察研究】CQ4

診療ガイドライン	急性胆管炎
対象	DICを伴う急性胆管炎
介入	トロンボモジュリン投与
対照	トロンボモジュリン非投与

*バイアスリスク、非直接性
　各ドメインの評価は"高(-2)"、"中/疑い(-1)"、"低(0)"の3段階
　まとめは"高(-2)"、"中(-1)"、"低(0)"の3段階でエビデンス総体に反映させる
** 上昇要因
　各項目の評価は"高(+2)"、"中(+1)"、"低(0)"の3段階
　まとめは"高(+2)"、"中(+1)"、"低(0)"の3段階でエビデンス総体に反映させる
各アウトカムごとに別紙にまとめる

アウトカム	DIC離脱率
個別研究	**バイアスリスク***

		バイアスリスク*							上昇要因**				非直接性*					リスク人数(アウトカム率)								
		選択バイアス	実行バイアス	検出バイアス	症例現象バイアス	その他																				
研究コード	**研究デザイン**	**背景因子の差**	**ケアの差**	**不適切なアウトカム測定**	**不完全なフォローアップ**	**不十分な交絡の調整**	**その他のバイアス**	**まとめ**	**量反応関係**	**効果減弱交絡**	**効果の大きさ**	**まとめ**	**対象**	**介入**	**対照**	**アウトカム**	**まとめ**	**対照群分母**	**対照群分子**	**(%)**	**介入群分母**	**介入群分子**	**(%)**	**効果指標(種類)**	**効果指標(値)**	**信頼区間**
Suetani	症例集積	-2	0	0	0	0	0	-2	0	0	0	0	0	0	0	0	0	36	19	52.8	30	25	83.3	N/A	N/A	N/A
Nakahara	症例集積	-2	-1	-2	0	0	0	-2	0	0	0	0	0	0	0	0	0	6	N/A	N/A	8	N/A	N/A	N/A	N/A	N/A

コメント(該当するセルに記入)

	抗DIC薬と抗菌薬に有意																									
	検定されていない。	他の抗DIC薬使用に	群別のmortalityが不明																							

【4-7 評価シート エビデンス総体】CQ4.

診療ガイドライン	急性胆管炎
対象	DICを伴う急性胆管炎
介入	トロンボモジュリン投与
対照	トロンボモジュリン非投与

エビデンスの強さはRCTは"強(A)"からスタート、観察研究は弱(C)からスタート
* 各ドメインは"高(-2)"、"中/疑い(-1)"、"低(0)"の3段階
** エビデンスの強さは"強(A)"、"中(B)"、"弱(C)"、"非常に弱(D)"の4段階
*** 重要性はアウトカムの重要性(1～9)

エビデンス総体

								リスク人数(アウトカム率)											
アウトカム	**研究デザイン/研究数**	**バイアスリスク***	**非一貫性***	**不精確***	**非直接性***	**その他(出版バイアスなど)***	**上昇要因(観察研究)***	**対照群分母**	**対照群分子**	**(%)**	**介入群分母**	**介入群分子**	**(%)**	**効果指標(種類)**	**効果指標統合値**	**信頼区間**	**エビデンスの強さ****	**重要性*****	**コメント**
Mortality	CS/2	-2	0	0	0	0	0	36	10	27.8	30	4	13.3	N/A	N/A	N/A	非常に弱(D)	8	
DIC離脱率	CS/2	-2	0	0	0	0	0	36	19	52.8	30	25	83.3	N/A	N/A	N/A	非常に弱(D)	8	

コメント(該当するセルに記入)

		背景因子に差																
		背景因子に差																

【5-1 推奨文章案】CQ4

1. CQ

抗菌薬と胆管ドレナージ以外に重症胆管炎に対して有効な治療は何か？

2. 推奨草案

DICを併発した重症胆管炎に対してトロンボモジュリン製剤の投与を考慮してもよい。

3. 作成グループにおける、推奨に関連する価値観や好み（検討した各アウトカム別に、一連の価値観を想定する）

本CQに対する推奨の作成に当たっては、重症胆管炎患者に対する死亡率の低下を重要視した。

4. CQに対するエビデンスの総括（重大なアウトカム全般に関する全体的なエビデンスの強さ）

□ A（強）　□ B（中）　□ C（弱）　☑ D（非常に弱い）

5. 推奨の強さを決定するための評価項目（下記の項目について総合して判定する）

推奨の強さの決定に影響する要因	判定	説明
アウトカム全般に関する全体的なエビデンスが強い ・全体的なエビデンスが強いほど推奨度は「強い」とされる可能性が高くなる。 ・逆に全体的なエビデンスが弱いほど、推奨度は「弱い」とされる可能性が高くなる。	□ はい ☑ いいえ	
益と害のバランスが確実（コストは含まず） ・望ましい効果と望ましくない効果の差が大きければ大きいほど、推奨度が強くなる可能性が高い。 ・正味の益が小さければ小さいほど、有害事象が大きいほど、益の確実性が減じられ、推奨度が「弱い」とされる可能性が高くなる。	☑ はい □ いいえ	

推奨の強さに考慮すべき要因
患者の価値観や好み、負担の確実さ（あるいは相違）
正味の利益がコストや資源に十分に見合ったものかどうかなど

重篤な有害事象が少ない。

明らかに判定当てはまる場合「はい」とし、それ以外は、どちらとも言えないを含め「いいえ」とする

ORIGINAL ARTICLE

Gut and Liver, Vol. 7, No. 3, May 2013, pp. 363-370

Use of Antithrombin and Thrombomodulin in the Management of Disseminated Intravascular Coagulation in Patients with Acute Cholangitis

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Background/Aims: To evaluate the usefulness and safety of treating disseminated intravascular coagulation (DIC) complicating cholangitis primarily with antithrombin (AT) and thrombomodulin (rTM). **Methods:** A DIC treatment algorithm was determined on the basis of plasma AT III levels at the time of DIC diagnosis and DIC score changes on treatment day 3. Laboratory data and DIC scores were assessed prospectively at 2-day intervals. **Results:** DIC reversal rates >75% were attained on day 7. In the DIC reversal group, statistically significant differences from baseline were observed in interleukin-6 and C-reactive protein levels within 5 days. Patients with no DIC score improvements after treatment with AT alone experienced slow improvement on a subsequent combination therapy with rTM. Although a subgroup with biliary drainage showed greater improvement in DIC scores than did the nondrainage subgroup, the mean DIC score showed improvement even in the nondrainage subgroup alone. Gastric cancer bleeding that was treated conservatively occurred in one patient. As for day 28 outcomes, three patients died from concurrent malignancies. **Conclusions:** Although this algorithm was found to be useful and safe for DIC patients with cholangitis, it may be better to administer rTM and AT simultaneously from day 1 if the plasma AT III level is less than 70%. **(Gut Liver 2013;7:363-370)**

Key Words: Disseminated intravascular coagulation; Cholangitis; Antithrombins; Thrombomodulin

INTRODUCTION

Excluding the treatment of the underlying disease, anticoagulants are the first-line therapy recommended in the Japanese Guideline for treatment of disseminated intravascular coagulation (DIC) caused by infections.[1] In the guideline, nevertheless, recombinant human soluble thrombomodulin (rTM), a novel agent for DIC, which first became available in Japan in 2008, is not cited. The proper use of rTM in combination with antithrombin (AT) and other currently used drugs for the treatment of DIC, and the safety and usefulness of combination therapy with rTM remain unclear.

Acute cholangitis (AC) is frequently complicated by DIC, a syndrome with a poor prognosis in severe cases. However, there have been few reports focusing on DIC treatment in AC.

Thus, we have devised an original algorithm of treatment primarily with AT and rTM that corresponds to changes in a patient's clinical status over time, which is minimally cumbersome. DIC was treated in patients with AC at our department employing this algorithm, whereby hematologic/blood biochemical data and changes in DIC score over time were evaluated to examine the usefulness and safety. This is the first part of a collective report on clinical experiences with rTM in the treatment of DIC complicating AC.

MATERIALS AND METHODS

1. Treatment algorithm for DIC

An algorithm for DIC treatment was developed on the basis of baseline plasma AT III level at the time of DIC diagnosis. On the basis of this algorithm, 1) AT was administered at 1,500 units/day for 3 days to patients showing a baseline plasma AT III level ≤69%. When there was still no improvement in score, as determined in accordance with the Japanese acute phase DIC diagnostic criteria (Table 1),[2] treatment with an rTM preparation at 380 units/kg/day was initiated on day 3; or 2) rTM at this dose was administered to patients with baseline plasma AT III levels ≥70%. AT administration of was terminated as deemed appro-

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priate when plasma AT III level was restored to ≥70%, and no additional AT treatment was administered even when plasma AT III level decreased to <70% during the treatment course, insofar as DIC score tended to improve. The rTM was administered at 130 units/kg/day in patients with renal dysfunction. The rTM preparation was administered intravenously over 30 minutes once daily, basically for 6 consecutive days. DIC treatment algorithms are summarized in Figs. 1 and 2. No heparin preparation was used because the anti-inflammatory effect of AT was inhibited by the concomitant use of heparin and because there was concern about adverse hemorrhagic reactions during treatment with multiple anticoagulants. No restriction was placed on other medications other than heparin for DIC, which were left to the discretion of attending physicians. Biliary drainage was performed as required according to the patient's condition, again on the basis of the attending physician's assessment. This study was conducted with the approval of the Ethics Committee of St. Marianna University School of Medicine Hospital.

Table 1. Disseminated Intravascular Coagulation Diagnostic Criteria Defined by the Japanese Association for Acute Medicine

	Score
Systemic inflammatory response syndrome (SIRS) criteria	
≥3	1
0–2	0
Platelet count, $\times 10^9$/L	
<80% or >50% decrease within 24 hr	3
≥80% and >120%; or >30% decrease within 24 hr	1
≥120	0
Prothrombin time (value of patient/nomal value)	
≥1.2	1
<1.2	0
Fibrin/fibrinogen degradation products, mg/L^{-1}	
≥25	3
≥10 and <25	1
<10	0
Diagnosis	
≥4 points	DIC

Fever of more than 38°C or less than 36°C. Heart rate of more than 90 beats per minute. Respiratory rate of more than 20 breaths per minutes or a $PaCO_2$ level of less than 32 mm Hg. Abnomal white blood cell count (>12,000/μL or <4,000/μL or >10% bands).

2. Patients

The study population consisted of 14 patients with AC complicated by DIC diagnosed at our department between April 2010 and March 2011. There were nine men and five women with a mean age of 72.5±8.4 years. Fourteen patients had AC; severe in 12 and moderate in two, as determined in accordance with the Japanese version of the Guideline for the Management of Acute Cholangitis (Table 2). The primary diseases underlying AC included malignant biliary tract stenosis in eight patients (carcinoma of the pancreatic head in five; bile duct carcinoma, hepatocellular carcinoma, and lymph node metastasis of gastric cancer in one each) and choledocholithiasis in six patients. DIC was diagnosed in accordance with the diagnostic criteria for acute-phase DIC (i.e., conditions were scored ≥4) (Table 1).[2] The DIC score at the time of diagnosis was four in five patients, five in three, six in four, seven in one, and eight in one. On the basis of the treatment algorithm, six patients were categorized into the AT-treated group, two into the rTM-treated group, and six into the group treated with the combination regimen of AT and rTM (AT+rTM-treated group). Other drugs administered concomitantly for DIC were gabexate mesilate in 13 patients and ulinastatin in four (including duplications). Endoscopic biliary drainage was performed in seven patients (endoscopic nasobiliary drainage [ENBD] in five and endoscopic biliary stenting (EBS) in two patients). Patient background characteristics are summa-

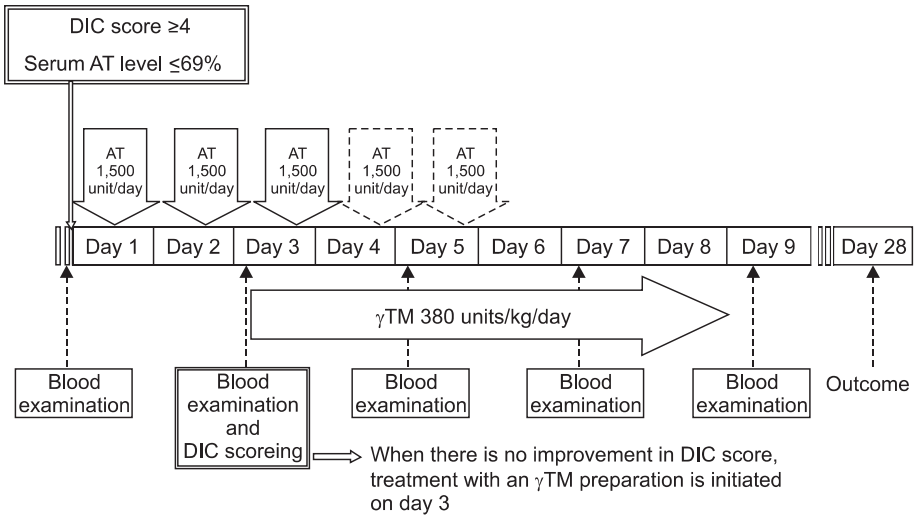

Fig. 1. Disseminated intravascular coagulation (DIC) treatment algorithm for patients with a baseline plasma antithrombin (AT) III level <69%.
γTM, thrombomodulin.

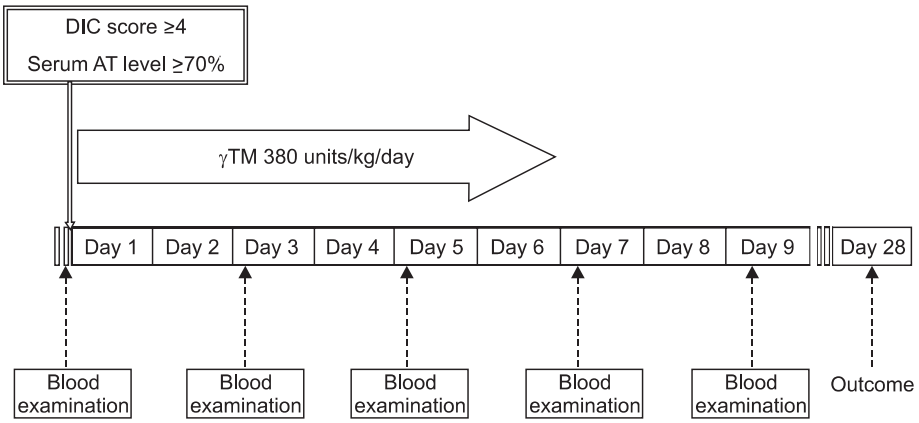

Fig. 2. Disseminated intravascular coagulation (DIC) treatment algorithm for patients with a baseline plasma antithrombin (AT) III level >70%.
γTM, thrombomodulin.

Table 2. The Severity Assessment Criteria for Acute Cholangitis of the Japanese Ministry of Health, Labor, and Welfare

"Severe" acute cholangitis is defined as acute cholangitis that is associated with at least one of the following factors:

1. Shock
2. Bacteremia
3. Disturbance of consciousness
4. Acute renal failure

"Moderate" acute cholangitis is defined as acute cholangitis that is associated with at least one of the following factors:

1. Jaundice (total serum bilirubin >2.0 mg/dL)
2. Hypoalbuminemia (serum albumin <3.0 g/dL)
3. Renal dysfunction (serum creatinine >1.5 mg/dL, serum urea nitrogen >20 mg/dL)
4. Throm bopenia (blood platelet count <120,000/mm^3)
5. Fever with temperatures above 39 degrees Celsius

"Mild" acute cholangitis is that which does not meet the criteria for "severe" or "moderate" acute cholangitis.

rized in Table 3.

3. Measurements

Taking the day of DIC diagnosis (treatment initiation day) as day 1, hematological/blood biochemical test findings (platelet count and levels of fibrin/fibrinogen degradation products [FDP], prothrombin time-international normalized ratio [PT-INR], fibrinogen [Fib], AT III, C-reactive protein [CRP], high mobility group box 1 [HMGB-1], and interleukin-6 [IL-6]) and DIC scores determined on the basis of the acute-phase DIC diagnostic criteria were assessed prospectively on days 1, 3, 5, 7, and 9 to verify therapeutic results on the basis of this treatment algorithm. Patients showing DIC score improvement to <3 were defined as the DIC reversal group. On the other hand, those showing DIC scores that remained at ≥4 were defined as the persistent DIC group. Therapeutic results were also assessed by comparison between the DIC reversal group and the persistent DIC group, among the AT-, rTM-, and AT+rTM-treated groups, and between biliary drainage and nondrainage groups. The patients were also assessed in terms of adverse events and clinical outcomes on day 28.

Platelet count and the levels of FDP, PT-INR, Fib, AT III, and CRP were measured as routine tests at our Central Clinical Laboratory. Samples for the determination of HMGB-1 and IL-6 levels were stored frozen at -80°C, and HMGB-1 level was assayed by ELISA (HMGB-1 ELISA Kit 2; Shino-Test Co., Kanagawa, Japan) and IL-6 level by CLEIRA (Quanti Glo Human IL-6 Immunoassay 2nd Generation; R&D Systems, MN, Minneapolis, USA).

4. Statistical analyse

Statistical analysis was carried out using the Prism5 program (GraphPad Software Inc., La Jolla, CA, USA). Intergroup comparison of median values of the hematological/blood chemical test parameters was performed using the Wilcoxon signed rank test. With respect to group mean DIC scores, the unpaired t-test with Welch's correction was carried out to compare between two groups, and one-way factorial ANOVA and multiple comparison tests were conducted to compare among three groups. Any intergroup differences found were considered to be statistically significant at $p<0.05$.

RESULTS

1. Time courses of changes in serum parameters and DIC score

The day of DIC diagnosis (treatment initiation day) was taken as day 1 for clarity. The median values of hematological/blood biochemical test results on days 1, 3, 5, 7, and 9 were respectively as follows: platelet counts, 9.7, 8.7, 9.7, 13.7, and $16.6\times10^4/\mu L$; FDP levels, 81.6, 66.2, 38.6, 25.1, and 26.1 μg/mL; PT-INR levels, 1.4, 1.3, 1.3, 1.3, and 1.3; Fib levels, 274, 345, 326, 325, and 295 mg/dL; AT III levels, 56%, 79%, 80%, 74%, and 70%; CRP levels, 11.9, 11.0, 5.3, 4.5, and 3.8 mg/dL; HMGB-1 levels, 15.7, 11.4, 10.6, 7.8, and 10.4 ng/mL; and IL-6 levels, 15,111.6, 106.0, 39.9, 34.3, and 36.5 pg/mL (Fig. 3).

Table 3. Patients Background Characteristics

Case	Diagnosis	Severity of acute cholangitis	DIC score	The dosing period of AT, day	The dosing period of rTM, day	Other medications for DIC	Biliary drainage
1	Pancreatic cancer	Severe	4	3	-	GM	-
2	Hepatocelluler carcinoma	Severe	4	5	-	GM, US	ENBD
3	Choledocholithiasis	Severe	5	3	3	GM	-
4	Pancreatic cancer	Severe	7	5	6	GM, US	-
5	Gastric cancer Lymph node metastasis	Severe	4	-	6	GM, US	-
6	Pancreatic cancer	Mild	7	3	6	GM	-
7	Choledocholithiasis	Severe	6	3	-	GM	ENBD
8	Pancreatic cancer	Mild	4	3	6	-	-
9	Choledocholithiasis	Severe	5	3	-	GM	ENBD
10	Cholangiocarcinoma	Severe	6	3	3	GM, US	ENBD
11	Choledocholithiasis	Severe	4	3	-	GM	ENBD
12	Choledocholithiasis	Severe	5	3	6	GM	EBS
13	Pancreatic cancer	Severe	6	3	-	GM	-
14	Choledocholithiasis	Severe	6	-	6	GM	EBS

DIC, disseminated intravascular coagulation; AT, antithrombin; rTM, thrombomodulin; GM, gabexate mesilate; US, ulinastatin; ENBD, endoscopic nasobiliary drainage; EBS, endoscopic biliary stenting.

Comparison between days 1 and 9 revealed statistically significant improvements in levels of CRP ($p<0.01$) and IL-6 ($p=0.02$). Mean acute-phase DIC score over time showed improvement, i.e., 5.3, 3.1, 2.6, 2.2, and 2.2 (Fig. 4), with a statistically significant difference between days 1 and 9 ($p<0.01$). The DIC reversal rate on days 9 was 78.6%.

2. Comparison between DIC reversal and persistent DIC groups

Median values of hematological/blood biochemical test results on days 1, 3, 5, 7, and 9 in the DIC reversal group (n=11) were respectively as follows: platelet counts, 9.7, 9.2, 13.2, 18.3, and $19.7\times10^4/\mu L$; FDP levels, 23.1, 8.1, 8.2, 8.2, and 12.8 μg/mL; PT-INR levels, 1.3, 1.1, 1.1, 1.1, and 1.1; Fib levels, 297.0, 395.0, 373.0, 407.0, and 329.5 mg/dL; AT III levels, 59.0%, 81.0%, 84.0%, 78.0%, and 71.0%; CRP levels, 15.6, 10.2, 4.0, 3.2, and 2.8 mg/dL; HMGB-1 levels, 17.5, 10.8, 9.1, 7.8, and 8.8 ng/mL; and IL-6 levels, 405.0, 44.1, 18.3, 15.7, and 16.6 pg/mL (Fig. 5). Comparison between days 1 and 9 revealed statistically significant improvements in the levels of CRP ($p<0.01$), HMGB-1 ($p=0.03$), and IL-6 ($p<0.01$). Statistically significant differences from baseline (day 1) were observed for IL-6 level ($p=0.02$) from day 3 onwards and for CRP level ($p<0.01$) from day 5 onwards, suggesting that these parameters may serve as predictive markers of early DIC improvement.

In the persistent DIC group (n=3), on the other hand, the median values on days 1, 3, 5, 7, and 9 were respectively as follows: platelet counts, 6.2, 2.3, 1.4, 1.2, and $2.9\times10^4/\mu L$; FDP levels, 58.2, 46.7, 31.7, 35.9, and 76.2 μg/mL; PT-INR levels, 1.3, 1.3, 1.3, and 1.5; Fib levels, 192.0, 211.0, 178.0, 178.0, and 174.0 mg/dL; AT III levels, 56.0%, 76.0%, 75.0%, 72.0%, and 59.0%; CRP levels, 5.0, 16.2, 5.4, 7.8, and 6.1 mg/dL; HMGB-1 levels, 7.6, 10.8, 9.7, 6.6, and 12.9 ng/mL; and IL-6 levels, 54.9, 50.3, 31.1, 25.5, and 75.2 pg/mL (Fig. 5). All of these parameters except AT III level showed worsening on day 9, as compared with those on day 1.

3. Comparisons among AT-, rTM-, and AT+rTM-treated groups

DIC score did not differ among the AT-, rTM-, and AT+rTM-treated groups at the start of treatment (day 1) ($p=0.40$), but differed significantly on day 3 ($p<0.01$), day 5 ($p<0.01$), and day 7 ($p=0.01$) (Fig. 6). Patients with a baseline AT III level ≤69% with no improvement in DIC score following 3-day AT medication showed slow improvement subsequent administration of rTM. There were no significant differences in DIC score ($p=0.05$) on day 9, and the findings suggest that rTM is effective for AT-resistant DIC albeit with slow responses to treatment.

4. Comparison between biliary drainage and nondrainage subgroups

Among the 14 patients with AC, the biliary drainage (n=7) and nondrainage (n=7) subgroups were compared. Successful endoscopic biliary drainage was performed in seven patients (ENBD in five and EBS in two patients). Reasons for nondrainage included failure to secure consent in five patients with advanced carcinoma, refusal in one, and technical failure in one. Baseline (day 1) DIC score did not differ significantly between

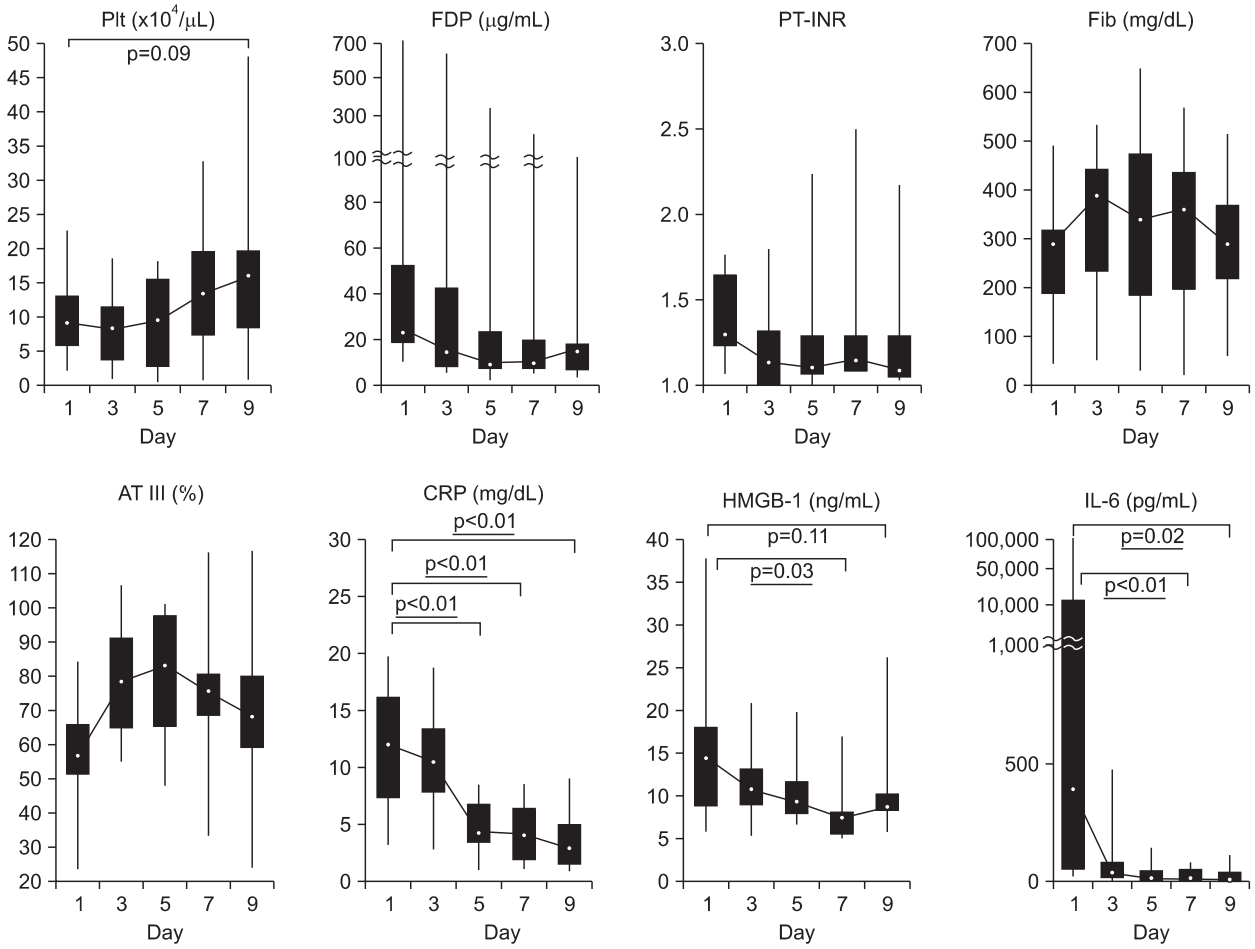

Fig. 3. Time courses of changes in the median values of parameters.
Plt, platelet count; FDP, fibrin/fibrinogen degradation product; PT-INR, prothrombin time-international normalized ratio; Fib, fibrinogen; AT III, antithrombin III; CRP, C-reactive protein; HMGB-1, high mobility group box 1; IL-6, interleukin-6.

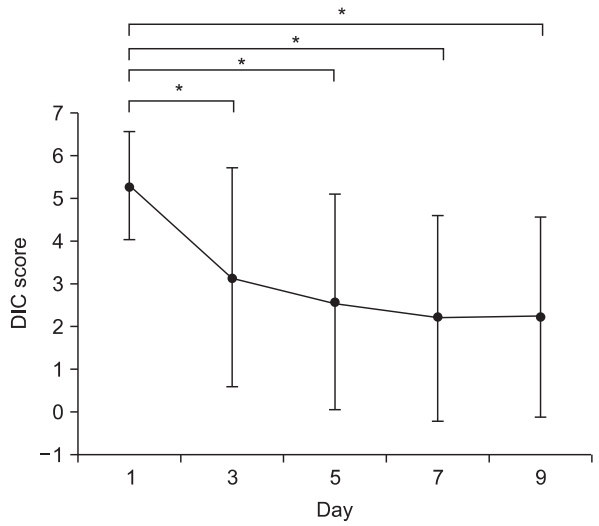

Fig. 4. Time course of changes in the mean values of disseminated intravascular coagulation (DIC) scores.
*p<0.01.

the biliary drainage and nondrainage subgroups (p=0.69), but patients receiving drainage showed a progressive improvement in DIC score, which significantly differed from that of the nondrainage group on day 9 (p=0.03) (Fig. 7). However, in the nondrainage subgroup, mean DIC score showed improvement on day 9 as compared with those on day 1.

5. Adverse events and outcomes

An adverse event occurred in one patient, i.e., bleeding from gastric cancer as a concurrent disease. This event was first observed in the form of tarry stools on day 6 of treatment with rTM, which required a 4-unit packed red cell transfusion, but hemostasis was achieved conservatively by discontinuation of rTM and administration of omeprazole. The outcome on day 28 after the start of treatment was survival in 11 patients and death in three. All three deaths were due to progression of malignant tumors as concurrent diseases.

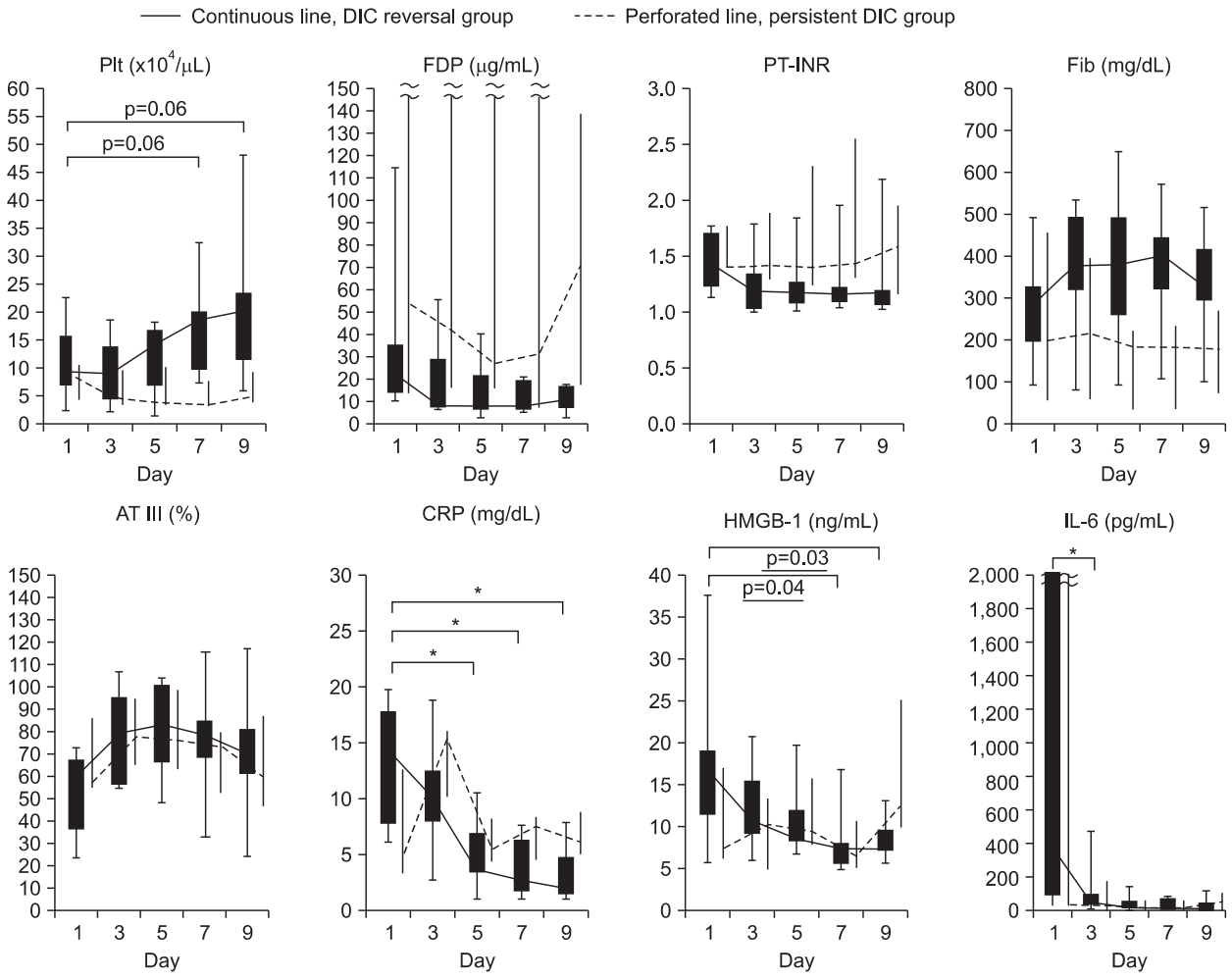

Fig. 5. Comparison of serum parameters between patients with disseminated intravascular coagulation (DIC) reversal and patients with sustained DIC.
Plt, platelet count; FDP, fibrin/fibrinogen degradation product; PT-INR, prothrombin time-international normalized ratio; Fib, fibrinogen; AT III, antithrombin III; CRP, C-reactive protein; HMGB-1, high mobility group box 1; IL-6, interleukin-6.
*p<0.01.

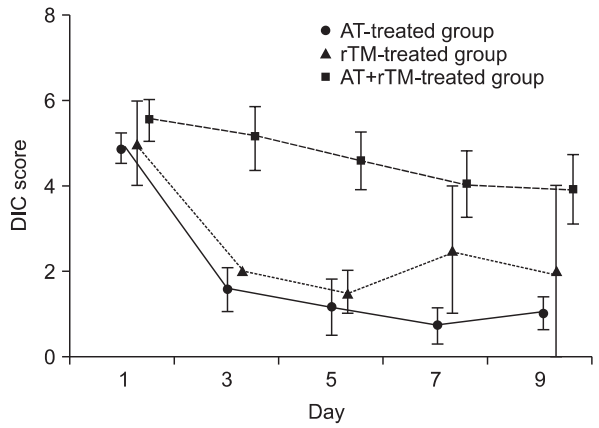

Fig. 6. Comparisons of disseminated intravascular coagulation (DIC) scores among antithrombin (AT)-, TM-, and AT+thrombomodulin (rTM)-treated groups.

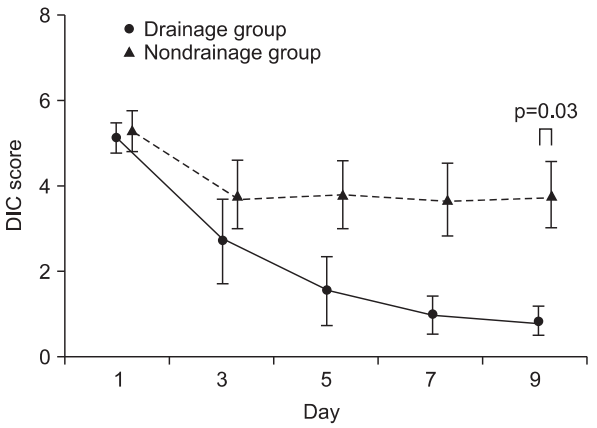

Fig. 7. Comparison of disseminated intravascular coagulation (DIC) scores between the biliary drainage and nondrainage subgroups.

DISCUSSION

The disease state of DIC in AC is of the hypercoagulable-hypofibrinolytic type, and excluding the treatment of the underlying disease, anticoagulants are the drugs mostly recommended in the Japanese Guideline for Treatment of DIC (grade of recommendation, A). Anticoagulant therapy with AT is the most highly recommended treatment (grade of recommendation, B1).[1]

AT is a physiological serine protease inhibitor that controls blood coagulation reactions mainly by inhibiting activated blood coagulation factor X and thrombin. Besides its anticoagulant activity, AT binds to heparin sulfate on vascular endothelial cells and promotes prostaglandin I2 production, thereby stabilizing activated neutrophils, and also binds to syndecan-4 in neutrophils, thereby decreasing the amount of chemokine receptors on the neutrophils. These events suppressing neutrophil chemotaxis produce anti-inflammatory effects.[3,4] In septicemic patients, severity grade reportedly shows an inverse correlation with plasma AT III level.[5] A large-scale clinical trial (KyberSept trial) in patients with severe sepsis showed no improvement of the prognosis with AT.[6] However, analysis of a subgroup of patients with concomitant DIC not treated with heparin among the study patients revealed a significant improvement in the outcome after 28 days as compared with that in a placebo group.[7]

Meanwhile, rTM has been available as a novel therapeutic agent for DIC since May 2008, making Japan the first country in the world to use this drug for DIC. Double-blind randomized clinical trials of rTM in Japan demonstrated its noninferiority to heparin.[8] Hence, a new treatment strategy for DIC is anticipated. The rTM is a drug produced by recombinant DNA technology using an extracellular domain containing the active moiety of rTM, a glycoprotein occurring on vascular endothelial cells, and rTM is a physiological anticoagulation factor that modulates blood coagulation *in vivo*.[9] The rTM activates protein C by reversibly binding to thrombin, and the activated protein C inhibits excessive thrombin production, eventually exerting an anticoagulant effect by suppressing the activation of the blood coagulation system.[10] Furthermore, it has been observed that rTM *per se* produces a direct anti-inflammatory effect, in that the lectin-like domain of rTM adsorbs HMGB-1 and thus exerts an anti-inflammatory effect by suppressing inflammatory cytokine production via stimulation of HMGB-1 lysis by thrombin.[11,12] A retrospective subgroup analysis of data from DIC patients with underlying infections also showed the usefulness of rTM.[13]

However, there is no consensus as yet regarding the use of this novel therapeutic agent, rTM, for DIC. The safety and usefulness of treatments combining AT and other drugs for DIC also remain to be clarified. There have been no reports documenting results of treatment primarily with AT and/or rTM particularly in DIC patients with AC. We therefore devised an original, minimally cumbersome algorithm that corresponds to changes in a patient's clinical status over time, whereby hematologic/blood biochemical data were prospectively obtained 2 days apart, and treatment results based on the algorithm were examined. For the diagnosis of DIC, there are three sets of diagnostic criteria: the Ministry of Heath, Labour and Welfare Diagnostic Criteria for DIC, the Diagnostic Criteria for Acute-Phase DIC, and the International Seciety on Thrombosis and Heamostasis Diagnostic Criteria. We employed the Diagnostic Criteria for Acute-Phase DIC, which is considered to be highly sensitive for DIC caused by infections and superior for early diagnosis although low in specificity.[2] With this treatment strategy, no heparin preparation was used because the anti-inflammatory effect of AT was reportedly inhibited by the concomitant use of heparin and because there was concern about adverse hemorrhagic reactions during treatment with multiple anticoagulants including rTM.[3] Since it is not covered by insurance if the plasma level of AT III is more than 70% in Japan, patients with baseline plasma AT III levels ≤69% were treated with AT, and those with baseline plasma AT III levels ≥70% were administered rTM. The patients were assessed again on day 3 of treatment and those exhibiting no improvement on AT therapy were administered rTM concomitantly thereafter. By day 7, about 80% of the patients had attained DIC reversal, suggesting the usefulness of this algorithm for treating DIC.

As an adverse event, hemostasis was achieved conservatively by discontinuation of rTM and administration of omeprazole. No other drug-related adverse events were observed, indicating the safety of this strategy. Nevertheless, the hemorrhage developed on day 6 of treatment with rTM in this case. As the duration of rTM treatment was specified as being up to 6 days in a Japanese phase III clinical trial of rTM,[8] it will be necessary to examine the safety of rTM administration for a longer period by assessing more cases.

Comparisons of responses among the three treatment groups revealed that the AT+rTM-treated group, in which rTM was combined with AT because patients showed no improvement in DIC score on day 3 of AT therapy, still showed a slower improvement in DIC score than the other two treatment groups, suggesting that these patients might be treatment-resistant. However, the difference between the DIC score of this combined regimen group and that of the other two groups tended to diminish progressively, suggesting the usefulness of rTM for treating AT-resistant DIC. It would be important to determine the optimal timing of instituting concomitant AT and rTM. In fact, the decision was made on day 3 or 4 of AT therapy in a study reported by Eguchi,[14] who stated that rTM is useful for AT-resistant DIC. However, as our results, it may be better to administer rTM and AT simultaneously from day 1 if the plasma level of AT III is less than 70%. Further investigation is necessary concerning the timing and dose among others in the AT+rTM regimen.

In this study, predictive markers of early DIC improvement

were examined. The results showed significant differences in IL-6 level and CRP level within the first 5 days of treatment between the reversed and persistent DIC groups. This finding suggests that these parameters might serve as predictive markers of early DIC improvement. With regard to prognostic markers of DIC exacerbation and the difference between the reversed and persistent DIC groups, on the other hand, evaluation was difficult because there were only three patients in the persistent DIC group, yet all the parameters other than AT III level worsened in this group. We also examined HMGB-1 level, which was first reported by Wang *et al*.[15] and has been drawing attention as a lethal mediator. A significant improvement in HMGB-1 level was noted in the DIC reversal group on day 7, as compared with the baseline value; whereas in the persistent DIC group, this parameter tended to worsen. Therefore, although this parameter cannot reliably be regarded as a predictive marker of an early therapeutic response, it is noteworthy that the worsening of HMGB-1 level was evident despite the improved or unchanged DIC score in the three patients who died from cancer within 28 days. Hence, the worsening of HMGB-1 level might be of value as an indicator of not only the exacerbation of DIC but also the worsening of the general condition.

Comparison between biliary drainage and those without, it revealed a significantly greater improvement in the drainage subgroup than the nondrainage subgroup. This implies that the treatment of cholangitis should be undertaken as aggressively as possible. In this study, in which a considerable proportion of patients had advanced carcinoma and not a few were reluctant to give consent for the drainage procedure, DIC score still tended to improve even among patients in the nondrainage subgroup. Althouh the biliary drainage as the treatment of underlying disease is the most important, it seems that this algorithm is effective especially with the cases who cannot be performed drainage.

Finally, it is necessary to consider that the results of the present manuscript contain biases such as the therapeutic efficacy of drugs, other than AT and rTM, that were used concomitantly, and that of biliary drainage. However, we believe that these observations will contribute to patient management in clinical settings, because this is the first part of a collective report on clinical experiences in using AT and rTM for the treatment of DIC complicating AC.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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ORIGINAL ARTICLE

Retrospective Study

Thrombomodulin in the management of acute cholangitis-induced disseminated intravascular coagulation

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Abstract

AIM: To evaluate the need for thrombomodulin (rTM) therapy for disseminated intravascular coagulation (DIC) in patients with acute cholangitis (AC)-induced DIC.

METHODS: Sixty-six patients who were diagnosed with AC-induced DIC and who were treated at our hospital were enrolled in this study. The diagnoses of AC and DIC were made based on the 2013 Tokyo Guidelines and the DIC diagnostic criteria as defined by the Japanese Association for Acute Medicine, respectively. Thirty consecutive patients who were treated with rTM between April 2010 and September 2013 (rTM group) were compared to 36 patients who were treated without rTM (before the introduction of rTM therapy at our hospital) between January 2005 and January 2010 (control group). The two groups were compared in terms of patient characteristics at the time of DIC diagnosis (including age, sex, primary disease, severity of cholangitis, DIC score, biliary drainage, and anti-DIC drugs), the DIC resolution rate, DIC score, the systemic inflammatory response syndrome (SIRS) score, hematological values, and outcomes. Using logistic regression analysis based on multivariate analyses, we also examined factors that contributed to persistent DIC.

RESULTS: There were no differences between the rTM group and the control group in terms of the patients' backgrounds other than administration. DIC resolution rates on day 9 were higher in the rTM group than in the control group (83.3% *vs* 52.8%, $P < 0.01$). The mean DIC scores on day 7 were lower in the rTM group than in the control group (2.1 ± 2.1 *vs* 3.5 ± 2.3, $P = 0.02$). The mean SIRS scores on day 3 were significantly lower in the rTM group than in the control group (1.1 ± 1.1 *vs* 1.8 ± 1.1, $P = 0.03$). Mortality on day 28 was 13.3% in the rTM group and 27.8% in the control group; these rates were not significantly different ($P = 0.26$). Multivariate analysis identified only the absence of biliary drainage as significantly associated with persistent DIC ($P < 0.01$, OR = 12, 95%CI: 2.3-60). Although the difference did not reach statistical significance, primary diseases (malignancies) ($P = 0.055$, OR = 3.9, 95%CI: 0.97-16) and the non-

use of rTM had a tendency to be associated with persistent DIC (P = 0.08, OR = 4.3, 95%CI: 0.84-22).

CONCLUSION: The add-on effects of rTM are anticipated in the treatment of AC-induced DIC, although biliary drainage for AC remains crucial.

Key words: Disseminated intravascular coagulation; Acute cholangitis; Thrombomodulin; Biliary drainage; Anticoagulant therapy

Core tip: To evaluate the need for thrombomodulin (rTM) in the management of acute cholangitis (AC)-induced disseminated intravascular coagulation (DIC), we retrospectively compared patients treated with rTM (rTM group) and without rTM (control group). DIC resolution rates were higher in the rTM group (P < 0.01). Multivariate analysis identified only the absence of biliary drainage as significantly associated with persistent DIC (P < 0.01), while there was a trend towards an association between persistent DIC and a lack of rTM (P = 0.08). Therefore, the add-on effects of rTM are anticipated in the treatment of AC-induced DIC, although biliary drainage remains crucial.

Suetani K, Okuse C, Nakahara K, Michikawa Y, Noguchi Y, Suzuki M, Morita R, Sato N, Kato M, Itoh F. Thrombomodulin in the management of acute cholangitis-induced disseminated intravascular coagulation. *World J Gastroenterol* 2015; 21(2): 533-540 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i2/533.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i2.533

INTRODUCTION

In recent years, there have been several reports on the efficacy of recombinant human soluble thrombomodulin (rTM) for the treatment of disseminated intravascular coagulation (DIC) associated with infection[1-4]. Various disorders that cause infections were described in these reports, but none of the studies focused on a single disease. Treatment of the primary disease causing DIC remains the most important factor in the resolution of the pathological conditions that underlie infectious DIC[5], and the prognosis of patients with DIC may be markedly affected by the outcome of treatment of the primary disease. Thus, it is crucial to focus on the primary disease to accurately assess the treatment outcomes of patients with infectious DIC.

In acute cholangitis (AC)-induced DIC, the treatment for AC, including biliary drainage, can immediate resolve DIC. However, some patients still have poor outcomes, and further improvements in therapy are needed. The utility of rTM for the treatment of DIC remains unclear. Our PubMed search on rTM therapy for AC-induced DIC, using terms such as "disseminated intravascular coagulation", "acute cholangitis", and "thrombomodulin", yielded only a single-arm case series that we previously reported[6]. We had reported favorable outcomes in patients who received a therapeutic regimen of rTM for AC-induced DIC. However, the prior series had a small sample size; in this study, we therefore compared a larger group of patients who were treated with and without rTM to evaluate the role of anti-DIC therapy with rTM for AC-induced DIC. This is the first comparative study of rTM in the treatment of AC-induced DIC.

MATERIALS AND METHODS

Patients

Thirty consecutive patients who were diagnosed as having AC-induced DIC and who were treated with rTM at St. Marianna University School of Medicine Hospital between April 2010 and September 2013 were enrolled in this study (rTM group). They were compared to 36 patients with AC-induced DIC who were treated without rTM (before the introduction of rTM therapy at our hospital) between January 2005 and January 2010. Detailed data were available from medical records, which allowed these 36 patients to serve as historical controls for the analysis (control group).

The rTM group included 22 men and 8 women with a mean age ± SD of 77.0 ± 7.7 years. AC was diagnosed and graded according to the 2013 Tokyo Guidelines[7] for the management of AC. AC was severe in 28 patients and moderate in 2 patients, while no patients had mild AC. The primary diseases causing AC were choledocholithiasis in 20 patients, malignant biliary stricture in 9 (pancreatic carcinoma in 5 patients, cholangiocarcinoma in 2, lymph node metastasis of gastric cancer in 1, and malignant lymphoma in 1), and primary sclerosing cholangitis in 1. Based on the DIC diagnostic criteria defined by the Japanese Association for Acute Medicine[8] (Table 1), DIC was diagnosed when the DIC score was 4 or above. The mean DIC score ± SD at the time of DIC diagnosis was 5.4 ± 1.4. The dose of rTM was 380 units/kg per day in 26 patients, while 4 patients received rTM at a reduced dose of 130 units/kg per day, due to renal dysfunction. The duration of rTM treatment was 6 d in all patients. Other anti-DIC drugs used (besides TM) were antithrombin (AT) in 26 patients, gabexate mesilate (GM) in 14 patients, and nafamostat mesilate (NM) in 4 patients (including duplicate counts). The antibiotics used were meropenem (MEPM) in 19 patients, sulbactam/cefoperazone (CPZ/SBT) in 5 patients, doripenem in 5 patients, and tazobactam/piperacilin (TAZ/PIPC) in 1 patient. Biliary drainage was performed in 25 patients but not in 5 patients. Of the patients who did not undergo biliary drainage, 4 patients did not consent, and the presence of cholangitis after the clearance of bile duct stones precluded this procedure in 1 patient.

Table 1 Diagnostic criteria for disseminated intravascular coagulation as defined by the Japanese Association for Acute Medicine

	Score
Systemic inflammatory response syndrome criteria[1]	
≥ 3	1
0-2	0
Platelet count (× 10^3/L)	
< 80 or > 50% decrease within 24 h	3
≥ 80 and < 120; or > 30% decrease within 24 h	1
≥ 120	0
Prothrombin time (Value of patient/Normal value)	
≥ 1.2	1
< 1.2	0
Fibrin/fibrinogen degradation products (mg/L)	
≥ 25	3
≥ 10 and < 25	1
< 10	0
Diagnosis	
≥ 4 points	DIC

[1]Systemic inflammatory response syndrome criteria: Fever of more than 38 ℃ or less than 36 ℃; Heart rate of more than 90 beats per min; Respiratory rate of more than 20 breaths per minute or a $PaCO_2$ level of less than 32 mmHg; Abnormal white blood cell count (> 12000/μL or < 4000/μL or > 10% bands). DIC: Disseminated intravascular coagulation.

The control group included 21 men and 15 women with a mean age ± SD of 75.7 ± 9.4 years. AC was severe in 32 patients and moderate in 4 patients, while no patients had mild AC. The primary diseases causing AC were choledocholithiasis in 19 patients, malignant biliary stricture in 15 patients (pancreatic carcinoma in 6, cholangiocarcinoma in 5, gallbladder cancer in 2, and hepatocellular carcinoma in 2), bilio-jejunal anastomotic stricture in 1, and bile duct stricture due to a hepatic cyst in 1 patient. The mean DIC score ± SD at the time of DIC diagnosis was 5.2 ± 1.2. The anti-DIC drugs used were GM in 30 patients, NM in 18, AT in 16, and danaparoid sodium (DS) in 6 (including duplicate counts). The antibiotics used were MEPM in 14 patients, SBT/CPZ in 14, imipenem/cilastatin in 7, and TAZ/PIPC in 1. Biliary drainage was performed in 24 patients.

Measurements

The rTM group of 30 patients and the control group of 36 patients were compared in terms of patient characteristics [including age, sex, primary disease (malignant/benign)], severity of cholangitis at the time of diagnosis, DIC score at the time of diagnosis, proportion of patients undergoing biliary drainage, and anti-DIC drugs, the DIC resolution rate, the DIC score, the systemic inflammatory response syndrome (SIRS) score, hematological values [platelet count (Plt), fibrin/fibrinogen degradation products (FDP), prothrombin time-international normalized ratio (PT-INR), fibrinogen (Fib), C-reactive protein (CRP), total bilirubin (T-bil)], and treatment outcomes. The day of DIC diagnosis and treatment initiation was designated as day 1, and hematological values were assessed on days 1, 3, 5, 7, and 9. Moreover, DIC resolution was defined as a decrease in the DIC score to 3 or less. The DIC and SIRS scores were expressed as mean ± SD, and hematological data were expressed as median values (quartiles).

A multinomial logistic regression analysis based on the univariate and multivariate analyses was used to identify factors that contributed to the failure of DIC resolution in patients with AC-induced DIC.

Written informed consent was obtained from all patients. This study was approved by the ethics committee of our hospital.

Statistical analysis

Statistical analyses were performed using the χ^2 test, Fisher's exact test, Welch's *t* test, the Mann-Whitney *U* test or the Wilcoxon single rank test, as appropriate. Variables that were found to have a potentially significant association with persistent DIC ($P < 0.2$) by univariate analysis were selected for entry into a multiple logistic regression model. *P* values < 0.05 were regarded as statistically significant. Statistical analyses were performed using the Prism 5 program (Graph Pad Software, Inc., CA, United States) and SPSS (version 19; SPSS, Chicago, IL, United States).

RESULTS

Patient characteristics

There were no significant differences between the rTM group and the control group with respect to age, sex, primary disease, severity of cholangitis, DIC score, SIRS score, or the proportion of patients who underwent biliary drainage at the time of DIC diagnosis. With regards to anti-DIC agents other than rTM that were used, the proportion of patients who received AT was significantly higher in the rTM group, while a higher proportion of patients in the control group received GM, NM and DS were higher (Table 2).

DIC resolution rate

The DIC resolution rate on day 9 was 83.3% (25/30) in the rTM group and 52.8% (19/36) in the control group (significantly higher in the rTM group; $P = 0.009$). The DIC resolution rates on day 7 were 76.7% (23/30) and 50.0% (18/36), respectively, and again, were significantly higher in the rTM group ($P = 0.041$).

DIC scores

Both the rTM and control groups showed a significant decrease in DIC scores from day 3 onward, compared to those on day 1. The comparison between the rTM and control groups revealed no difference in the mean DIC scores at the time of diagnosis, which were 5.4 ± 1.4 in the rTM group and 5.2 ± 1.2 in the control group ($P = 0.524$). However, the mean DIC scores on day 7 were 2.1 ± 2.1 and 3.5 ± 2.3 ($P = 0.018$), and the mean DIC scores on day 9 were 1.8 ± 1.9 and 3.3 ± 2.4, respectively ($P = 0.009$). The mean DIC scores on days 7 and 9 were

Table 2 Comparison of patient characteristics between the recombinant human soluble thrombomodulin and control groups

	rTM group (n = 30)	Control group (n = 36)	P value
Age (yr)	77.0 ± 7.7	75.7 ± 9.4	0.554
Sex (Male/Female)	22/8	21/15	0.203
Primary disease (Benign/Malignant)	21/9	21/15	0.327
Severity of cholangitis (Severe/Moderate)	28/2	32/4	0.845
DIC score	5.4 ± 1.4	5.2 ± 1.2	0.523
SIRS score	2.4 ± 1.3	2.6 ± 1.0	0.599
Biliary drainage	25	24	0.123
Anticoagulant drug			
AT	26	16	< 0.001
GM	14	30	0.002
NM	4	18	0.004
DS	0	6	0.019
Antibiotics			
MEPM	19	14	0.048
IPM/CS	0	7	0.031
DRPM	5	0	0.037
SBT/CPZ	5	14	0.047
TAZ/PIPC	1	1	0.556

DIC: Disseminated intravascular coagulation; SIRS: Systemic inflammatory response syndrome; rTM: Recombinant human soluble thrombomodulin; AT: Antithrombin; GM: Gabexate mesilate; NM: Nafamostat mesilate; DS: Danaparoid sodium; MEPN: Meropenem; IPM/CS: Imipenem/Cilastatin; DRPM: Doripenem; SBT/CPZ: Sulbactam/Cefoperazone; TAZ/PIPC: Tazobactam/Piperacilin.

significantly lower in the rTM group (Figure 1A).

SIRS scores

Compared to day 1, both the rTM and control groups showed a significant decrease in SIRS scores from day 3 onward. There were no differences between the rTM and control groups in terms of the mean SIRS scores at the time of diagnosis, which were 2.4 ± 1.3 in the rTM group and 2.6 ± 1.0 in the control group (P = 0.599). However, the scores on day 3 were 1.1 ± 1.1 and 1.8 ± 1.1 (P = 0.027), respectively, and were significantly lower in the rTM group. Subsequently, the mean SIRS scores in the rTM group remained significantly lower (Figure 1B).

Hematological values

The median hematological values (day 1/day 9) in the rTM group were as follows: Plt, 70.5 (58.8-94.0)/182.0 (80.5-266.5) × 10^3/μL (P < 0.001); FDP, 20.8 (10.8-43.2)/8.8 (5.9-17.9) μg/mL (P = 0.010); PT-INR, 1.27 (1.21-1.52)/1.18 (1.14-1.24) (P = 0.024); Fib, 293.5 (203.5-449.3)/373.0 (284.8-452.3) mg/dL (P = 0.092); CRP, 8.9 (5.9-15.1)/3.6 (2.0-7.8) mg/dL (P < 0.001); and T-bil, 3.8 (1.8-5.4)/1.9 (1.2-3.1) mg/dL (P = 0.023). The Plt, FDP, PT-INR, CRP, and T-bil values on day 9 showed significant improvement compared to those on day 1. In contrast, the median hematological values (day 1/day 9) in the control group were as follows: Plt, 88.5 (70.3-134.5)/155.0 (73.3-249.0) × 10^3/μL (P = 0.024); FDP, 35.4 (14.0-51.5)/21.0 (11.2-36.5) μg/mL (P = 0.155); PT-INR, 1.34 (1.24-1.67)/1.21 (1.08-1.47) (P = 0.054); Fib, 399.0 (243.0-464.0)/302.0 (219.0-445.5) mg/dL (P = 0.180); CRP, 13.6 (9.8-18.2)/4.8 (2.1-8.1) mg/dL (P < 0.001); and T-bil, 4.0 (1.9-6.7)/1.7 (1.1-4.7) mg/dL (P = 0.021). The Plt, CRP and T-bil values on day 9 showed significant improvement compared to the Day 1 values. A comparison of the median hematological values between the rTM and control groups showed that, although the levels of Plt on day 1 were significantly lower in the rTM group (P = 0.023), the levels of Plt on day 9 were higher in the rTM group; this difference did not reach statistical significance (P = 0.699). Although there was no difference in FDP on day 1 (P = 0.157) between the two groups, from day 3 onward (P = 0.045), the level of FDP was significantly lower in the rTM group. The fluctuations in median hematological values are shown in Figure 1C.

Outcomes

The mortality rate on day 28 was 13.3% (4/30) in the rTM group and 27.8% (10/36) in the control group; although mortality was higher in the control group, the difference did not reach statistical significance (P = 0.260). In the rTM group, all 4 deaths were classified as due to malignant tumors. Of the 10 deceased patients in the control group, cancer deaths occurred in 7 patients, and deaths due to worsening DIC were observed in the remaining 3 patients.

Factors contributing to the failure of DIC resolution

The univariate analysis identified primary disease (malignancy) (P = 0.003, OR = 5.3, 95%CI: 1.8-16), absence of biliary drainage (P < 0.001, OR = 16, 95%CI: 3.9-66), non-use of rTM (P = 0.010, OR = 4.5, 95%CI: 1.5-14), and non-use of NM (P = 0.016, OR = 0.26, 95%CI: 0.088-0.76) as factors that significantly contributed to persistent DIC (Table 3). A multivariate analysis was performed, incorporating the factors that were identified by univariate analysis, as well as the non-use of GM (P = 0.107) and Fib < 200 mg/dL (P = 0.186), both of which were factors with P values < 0.2 in the univariate analysis; the absence of biliary drainage (P = 0.003, OR = 12, 95%CI: 2.3-60) was the only factor that was found to contribute to persistent DIC (Table 4). Although the difference did not reach statistical significance, it was observed that primary disease (malignancies) (P = 0.055, OR = 3.9, 95%CI: 0.97-16) and non-use of rTM (P = 0.080, OR = 4.3, 95%CI: 0.84-22) tended to be associated with persistent DIC.

DISCUSSION

Since May 2008, rTM has been available in Japan as a novel therapeutic agent for DIC. In recent years, there have been several reports on the efficacy of rTM, which binds to thrombin and activates protein C to exert an anticoagulant effect[9,10], for the treatment of infectious

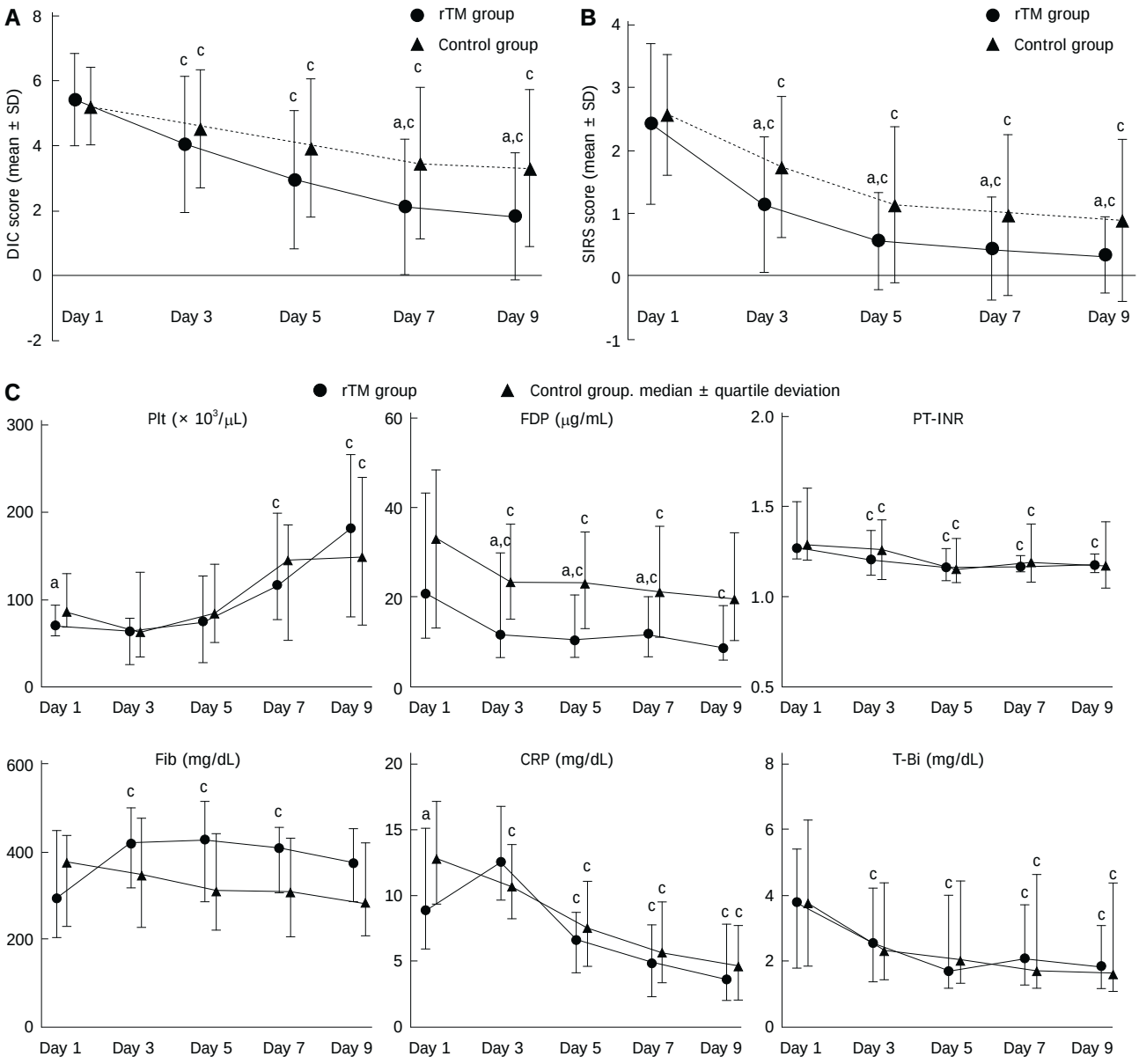

Figure 1 Comparison of the mean values of the disseminated intravascular coagulation scores (A), the systemic inflammatory response syndrome scores (B) and serum parameters between the recombinant human soluble thrombomodulin group and the control group (C). [a]*P* < 0.05 *vs* control group; [c]*P* < 0.05 *vs* baseline. DIC: Disseminated intravascular coagulation; rTM: Recombinant human soluble thrombomodulin; SIRS: Systemic inflammatory response syndrome; FDP: Fibrin/fibrinogen degradation products; PT-INR: Prothrombin time-international normalized ratio; Fib: Fibrinogen; CRP: C-reactive protein; T-Bil: Total bilirubin.

DIC[1-4]. In addition to this anticoagulant effect, rTM also elicits an indirect anti-inflammatory effect through activated protein C[9,11-13] and thrombin-activatable fibrinolysis[14,15]. Moreover, rTM exerting a direct anti-inflammatory effect by deactivating high mobility group box 1[16-18] and lipopolysaccharide[19] by binding to these molecules with the lectin-like domain of rTM. Thus, rTM has great potential as a drug for the treatment of infectious DIC.

However, the treatment of the underlying disease causing DIC is essential to achieve resolution of the pathological conditions that are associated with infectious DIC[5]. This is especially relevant in AC-induced DIC, where immediate biliary drainage can lead to prompt resolution of the DIC. Better therapies are needed, as there are still some DIC patients with poor outcomes; however, the usefulness of anti-DIC therapy with rTM remains unclear. Thus, we conducted the present study in patients with AC-induced DIC to evaluate the role of anti-DIC therapy with rTM by comparing outcomes between patients who did and did not receive rTM treatment.

Although there were no differences between the two groups in terms of age, sex, primary disease, severity of cholangitis, DIC score, or in the proportion of patients who underwent biliary drainage, the proportion of patients who received AT was significantly larger in the rTM group. However, the possibility of bias due to the therapeutic effects of AT must be taken into consideration when interpreting therapeutic outcomes in

Table 3 Factors associated with persistent disseminated intravascular coagulation (univariate analysis)

	Persistent DIC (n = 25)	Resolved DIC (n = 41)	P value	OR (95%CI)
Age (> 80 yr)	9	18	0.610	0.72 (0.26-2.0)
Female	7	16	0.431	0. 61 (0.21-1.8)
Primary disease (Malignant)	15	9	0.003	5.3 (1.8-16)
Severity of cholangitis (Severe)	23	37	1.000	1.2 (0.21-7.3)
DIC score (> 6)	12	15	0.442	1.6 (0.58-4.4)
SIRS score (> 3)	11	24	0.313	0.56 (0.20-1.5)
Without biliary drainage	14	3	< 0.001	16 (3.9-66)
Without rTM	19	17	0.010	4.5 (1.5-14)
Without AT	12	13	0.203	2.0 (0.71-5.5)
Without GM	5	17	0.107	0.35 (0.11-1.1)
Without NM	12	32	0.016	0.26 (0.088-0.76)
Without DS	22	37	1.000	0.79 (0.16-3.9)
Plt (< 80 × 10^3/μL)	12	24	0.452	0.65 (0.24-1.8)
FDP (> 25 μg/mL)	17	20	0.201	2.2 (0.79-6.3)
PT-INR	10	12	0.426	1.6 (0.57-4.6)
Fib (< 200 mg/dL)	7	5	0.186	2.8 (0.78-10)
CRP (> 15 mg/dL)	7	14	0.786	0.75 (0.25-2.2)
T-Bil (> 10 mg/dL)	4	3	0.412	0.49 (0.35-12)

DIC: Disseminated intravascular coagulation; SIRS: Systemic inflammatory response syndrome; rTM: Recombinant human soluble thrombomodulin; AT: Antithrombin; GM: Gabexate mesilate; NM: Nafamostat mesilate; DS: Danaparoid sodium; Plt: Platelet count; FDP: Fibrin/fibrinogen degradation products; PT-INR: Prothrombin time-international normalized ratio; CRP: C-reactive protein; Fib: Fibrinogen; T-Bil: Total bilirubin.

Table 4 Factors associated with persistent disseminated intravascular coagulation (multivariate analysis)

	P value	OR (95%CI)
Primary disease (Malignant)	0.055	3.9 (0.97-16)
Without biliary drainage	0.003	12 (2.3-60)
Without rTM	0.080	4.3 (0.84-22)
Without GM	0.680	1.5 (0.25-8.5)
Without NM	0.188	0.37 (0.083-1.6)
Fib (< 200 mg/dL)	0.403	2.2 (0.35-14)

rTM: Recombinant human soluble thrombomodulin; GM: Gabexate mesilate; NM: Nafamostat mesilate; Fib: Fibrinogen.

the rTM group. According to the Japanese guidelines for DIC treatment, which were prepared in 2009[5], AT is the most strongly recommended of all anti-DIC drugs. In the rTM group, which included patients who were treated in 2010 and thereafter, a higher frequency of AT use can be expected as a background condition. Because only a short time has elapsed since rTM became available, it is not included in the Japanese guidelines for DIC treatment. There have been many reports on the effectiveness of AT for the treatment of infectious DIC[20]. However, the KyberSept trial, reported in 2001[21], showed that the use of AT is not associated with decreased mortality, and the European guidelines for DIC treatment recommend restraint in the use of AT for the treatment of infectious DIC[22,23]. Our present univariate analysis identified only the use of rTM as a contributory factor in the successful treatment of DIC, while AT was not identified as such a factor. However, further studies are needed to determine the usefulness of AT for the treatment of AC-induced DIC; due to the retrospective nature of this study, we were unable to evaluate serum AT Ⅲ values in our patients.

The DIC resolution rate was significantly higher in the rTM group than in the control group, suggesting that rTM is highly effective for the treatment of AC-induced DIC. Although significant decreases in the DIC and SIRS scores from day 1 to day 3 were observed in both the rTM group and in the control group, a comparison between these two groups revealed that the DIC and SIRS scores had been significantly lower since days 7 and 3, respectively, in the rTM group and that greater improvements in the scores were observed in this group. The SIRS scores in particular were significantly improved in the early phase of treatment in the rTM group, which may be attributable to the anti-inflammatory effect of rTM[9,11-19]. With respect to the hematological findings, the control group showed significant improvements in Plt, CRP, and T-bil from day 1 to day 9, whereas the rTM group showed significant improvements in coagulation markers, such as FDP and PT-INR, in addition to Plt, CRP and T-bil. Although Plt levels on day 1 were significantly lower in the rTM group than in the control group, the Plt values on day 9 were higher in the rTM group. However, these differences did not reach statistical significance. Although there was no difference in FDP between the two groups on day 1, the levels of FDP were significantly lower from day 3 onward in the rTM group. These results suggest that rTM exerts a favorable anticoagulant effect. Thus, it is possible that in patients with AC-induced DIC, earlier and more marked resolution of the pathological condition may occur with the use of rTM.

There was no statistically significant difference in the mortality rate on day 28 between the two groups. However, the causes of death in all 4 patients in the rTM group were classified as malignant tumors, but the causes of death in 3 of the 10 deceased patients in

the control group were classified as being DIC-related. Based on these results, we can reasonably speculate that the resolution of DIC by rTM administration may have contributed to improved outcomes. In fact, there are reports on septic DIC describing reduced mortality at 28 d after the initiation of treatment with rTM[2,24,25]. In the present study, there were only 3 DIC-related deaths. To examine the effects of rTM on the improvement of the outcomes of patients with AC-induced DIC, multicenter studies with a larger sample size are needed.

In the present study, a multivariate analysis was performed to identify factors that contributed to persistent DIC. The absence of biliary drainage was identified as the only factor that contributed to persistent DIC. The treatment of the underlying disease causing DIC is considered to be the most important aspect of the treatment of infectious DIC[5], and the results of our study support this concept. Specifically, in patients with AC, a complete response is often achieved by biliary drainage[26,27], which is clearly the most important procedure for the clinical management of DIC. We advocate that biliary drainage be performed whenever possible. Furthermore, although the difference was not statistically significant, we observed that the non-use of rTM also tended to be associated with persistent DIC (P = 0.080, OR = 4.3, 95%CI: 0.84-22). It appears that treatment can be optimized by a combination of biliary drainage and the use of rTM. Moreover, our multivariate analysis revealed that the presence of malignant tumors also tended to be associated with persistent DIC, presumably because neoplastic as well as infectious DIC influenced the outcomes of patients in our study. Future studies are eagerly anticipated regarding the effects of rTM on neoplastic DIC due to solid cancers.

In conclusion, although biliary drainage for acute cholangitis is the most important treatment for AC-induced DIC, the use of rTM can lead to an earlier and more marked improvement in DIC and SIRS scores, which may improve clinical outcomes. However, to further examine the effects of rTM on the improvement of the outcomes of patients with AC-induced DIC, additional multicenter studies with a larger sample size are needed.

COMMENTS

Background

In acute cholangitis (AC)-induced disseminated intravascular coagulation (DIC), treatment for AC, including biliary drainage, can achieve resolution of the DIC. However, further improvements in treatment are needed, as there are still patients with poor outcomes.

Research frontiers

There have been several reports on the efficacy of recombinant human soluble thrombomodulin (rTM) for DIC that is associated with infection. However, in AC-induced DIC, the usefulness of anti-DIC therapy with rTM remains unclear.

Innovations and breakthroughs

The authors compared patients treated with rTM (rTM group) and without rTM (control group) to evaluate the role of anti-DIC therapy with rTM for AC-induced DIC. DIC resolution rates were higher in the rTM group (P < 0.01), and DIC scores were lower in the rTM group (P < 0.01). Multivariate analysis identified only the absence of biliary drainage as a contributor to the failure of DIC resolution (P < 0.01), and the non-use of rTM also tended to contribute to failure of DIC resolution (P = 0.08).

Applications

The add-on effects of rTM are anticipated in the treatment of AC-induced DIC, although biliary drainage for AC remains crucial.

Peer review

This paper is the first to demonstrate the effectiveness of rTM in cases of DIC due to acute cholangitis. Biliary drainage is the most effective procedure for the control of DIC, but rTM improves outcomes for patients. This retrospective study is original with solid data that is well analyzed.

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