Results-2

Hb基準値を変動（10→9g/dL）させた時の疑い症例

Characteristics of suspected AGRA patients

No.	Gender	Age	ANC(/μL)	PLT(10^4/μL)	Hb(g/dL)	Suspected Drug
1	Female	34	322	24.3	11.5	MMI PTU
2	Female	49	455	21.3	11.3	MMI PTU
3	Male	51	0	41.7	15.8	MMI
4	Female	73	140	33.6	**9.3**	Ticro
5	Female	23	9	38.4	**9.9**	SASP

Expert judge

検索アルゴリズムの性能を評価するために、真の薬剤性無顆粒球症患者を同定する必要がある。

カルテ調査を行い、専門医による確定診断を実施した。

7名の真の薬剤性無顆粒球症患者を同定

Evaluation of Algorithm

Evaluation of Algorithm in case of Hb≧**10**g/dL

アルゴリズム	副作用あり	副作用なし	計
陽性	3	0	3
陰性	4	2249	2253
計	7	2249	2256

PPV =1.000(3/3)
NPV =0.998(2249/2253)
感度 =**0.429**(3/7)
特異度 =1.000(2249/2249)

Evaluation of Algorithm in case of Hb≧**9**g/dL

アルゴリズム	副作用あり	副作用なし	計
陽性	5	0	5
陰性	2	2249	2251
計	7	2249	2256

PPV =1.000(5/5)
NPV =0.999(2249/2251)
感度 =**0.714**(5/7)
特異度 =1.000(2249/2249)

処方データと検査値データのみから、感度70%のアルゴリズムを作成することができた。

Discussion

- 無顆粒球症の定義は「ANC<500/μL」であるが、HbやPLT、投与期間、最終投与日から発症までの期間がアルゴリズムの感度・特異度に影響を与えると考えられる。実際にHbの基準値を変えることで疑い症例が3名から5名に増加した。
- 今後は、今回作成したアルゴリズムを他の大学病院のDBに適応し、検証的解析を行う。
- 本研究では、1施設のデータを基にして、検査値、期間等の閾値を設定した。従って、規模や機能の異なる他施設のデータを用いる場合には、閾値を再検討する必要がある。

Conclusion

- アルゴリズム内の基準値を変動させることで、最適なカットオフ値をもつ検索式構築のための条件を設定することが可能となった。
- 今回用いたアルゴリズムについて、全てのステップのSASプログラミング化が可能であり、データフォーマットを統一することで、自動的、簡便に疑い症例を抽出することが可能となった。

Identification of Drug-Induced Liver Injury in Medical Information Databases Using the Japanese Diagnostic Scale [779]

Tadaaki Hanatani[1,2], Kimie Sai[1], Masahiro Tohkin[2], Katsunori Segawa[1], Michio Kimura[3], Katsuhito Hori[4], Junichi Kawakami[4] and Yoshiro Saito[1]

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ABSTRACT

Background: Challenges using medical information databases (MIDs) for identifying drug-induced liver injury (DILI) have been addressed worldwide. Because of diagnostic complexity, a standardized method for DILI detection has not yet been established. ***Objectives:*** We aimed to develop a DILI detection algorithm based on the Digestive Disease Week Japan 2004 (DDW-J) scale, a Japanese clinical diagnostic criteria for DILI. We then compared the findings between the DDW-J and the Council for International Organizations of Medical Sciences/the Roussel Uclaf Causality Assessment Method (CIOMS/RUCAM) scales to confirm its consistency. Possible risk factors for DILI were assessed using the DDW-J algorithm. ***Methods:*** Using an MID from Hamamatsu University Hospital, we constructed DDW-J and CIOMS/RUCAM algorithms and compared the judgments based on the two algorithms. We examined characteristics of DILI cases identified by the DDW-J algorithm after antibiotic treatment, and evaluated possible risk factors for DILI by multivariate logistic regression analysis in the Hamamatsu population and a second population that included data from 124 hospitals, which was derived from an MID from Medical Data Vision Co., Ltd. ***Results:*** The concordance rate was 79.4% between DILI patients identified by the DDW-J and CIOMS/RUCAM algorithms; the Spearman rank correlation coefficient was 0.952 ($P < 0.0001$). Men showed a significantly higher risk for DILI after antibiotic treatments in both MID populations. ***Conclusions:*** We have developed a useful DILI detection method based on the DDW-J scale using MIDs, which was compatible with the international standardized scale. This study provides evidence for the utility of MID-based research for improving pharmacovigilance.

METHODS

This study was approved by the ethics committees of the National Institute of Health Sciences and Hamamatsu University School of Medicine .

1. Data Sources (MIDs) in Japan

Hamamatsu; Hamamatsu University Hospital (April 1,2007 to March 31, 2012)

MDV (Medical Data Vision Co., Ltd.); 124 hospitals (April 1, 2008 to August 31, 2011)

2. Study drugs

Clarithromycin (CM), azithromycin (AM), levofloxacin (LX), moxifloxacin (MX)

3. DILI detection algorithm

1) Eligibility criteria

2) Liver Injury and classification

Liver injury definition: ALT > 2xULN or ALP > ULN

Hepatocellular type	ALT > 2xULN and ALP ≤ULN, or R >5
Cholestatic type	ALT ≤ ULN and ALP > 2xULN, or R ≤2
Mixed type	ALT > 2xULN, ALP > ULN, and R >2 and <5

R = (ALT/ULN)/(ALP/ULN)

3) DILI detection based on DDW-J2004 and CIOMS/RUCAM scales

The DDW-J 2004 scoring was applied to the DILI detection algorithm (DDW-J), and the algorithm based on the CIOMS/RUCAM scale (CIOMS/RUCAM) was compared as a reference. DILI was defined as a total score ≥5 in the DDW-J, and ≥6 in the CIOMS/RUCAM algorithm, respectively (Table 1).

3. Comparison of DDW-J and CIOMS/RUCAM algorithms

Because the CIOMS/RUCAM scale excludes the delayed onset cases except when dealing with slowly metabolized chemicals (Table 1), the comparison of DDW-J and CIOMS/RUCAM algorithms was performed in the non-delayed onset population (Fig. 1).

4. Multivariate analysis on risk factors

To evaluate the risk factors associated with DILI after treatment with the study drugs, a multivariate logistic regression analysis was performed adjusting for age (≥55 years), gender, in/outpatient status, diabetes mellitus, treatment duration, and high dose.

Table 1. DDW-J2004 and CIOMS/RUCAM scoring systems applied to DILI detection algorithm

	Hepatocellular Type		Cholestatic or Mixed Type		Score DDW-J	Score CIOMS/RUCAM
1. Time to onset after treatment	**Initial**	**Subsequent**	**Initial**	**Subsequent**		
From the beginning of the drug	5 - 90 days	1 - 15 days	5 - 90 days	1 - 90 days	+ 2	+ 2
	< 5 or > 90 days	> 15 days	< 5 or > 90 days	> 90 days	+ 1	+ 1
From cessation of the drug	≤ 15 days	≤ 15 days	≤ 30 days	≤ 30 days	+ 1	+ 1
Delayed onset[a]	> 15 days	> 15 days	> 30 days	> 30 days	0	
[a] In the CIOMS/RUCAM scale, the delayed onset case of DILI is considered 'unrelated' except for slowly metabolized chemicals						
2. Course	**Change in ALT between peak value**		**Change in ALP (or total bilirubin)***			
After stopping the drug:	Decrease ≥50% within 8 days		Not applicable		+ 3	+ 3
	Decrease ≥50% within 30 days		Decrease ≥50% within 180 days		+ 2	+ 2
	Not applicable		Decrease <50% within 180 days		+ 1	+ 1
	No info/decrease ≥50% after 30 days		Persistence/increase/no info			0
	No info/decrease <50% within 30 days		Persistence/increase/no info		0	
	Decrease <50% after 30 days/recurrent		Not applicable		− 2	− 2
	If the drug is continued:				0	0
3. Risk factors	**Alcohol**		**Alcohol or Pregnancy**			
Alcohol or Pregnancy**	Presence		Presence		+ 1	+ 1
	Absence		Absence		0	0
Age	≥ 55 years		≥ 55 years			+ 1
	< 55 years		< 55 years			0
4. Concomitant drug(s)**						
	None/no info/concomitant drug with incompatible time to onset					0
	Concomitant drug with suggestive or compatible time to onset					− 1
	Concomitant drug known to be hepatotoxic with a suggestive time to onset					− 2
	Concomitant drug with clear evidence for its role					− 3
5. Exclusion of other causes of liver injury						
Group I (6 causes): HAV, HBV, HCV, biliary diseases, alcoholism, shock	All causes in Group I and II ruled out				+ 2	+ 2
	The 6 causes of Group I ruled out				+ 1	+ 1
Group II: CMV, EBV (HSV, complications: autoimmune hepatitis, chronic hepatitis B or C, etc.)*	Five or 4 causes of Group I ruled out				0	0
	Less than 4 causes of Group 1 ruled out				− 2	− 2
	Non drug cause highly probable				− 3	− 3
6. Previous information on hepatotoxicity of the drug						
	Reaction labeled in the product characteristics				+ 1	+ 2
	Reaction published but unlabeled				+ 1	+ 1
	Reaction unknown				0	0
7. Eosinophilia						
≥ 5% increase	Presence				+ 1	
	Absence				0	
8. Drug lymphocyte stimulation test (DLST)**						
	Positive				+ 2	
	False-positive				+ 1	
	Negative OR No-test				0	
9. Response to readministration						
with suspected drug alone	Doubling of ALT		Doubling of ALP or bilirubin		+ 3	+ 3
with another drug given at initial injury	Doubling of the ALT		Doubling of the ALP or bilirubin		+ 1	+ 1
with the same condition (with suspected drug alone)*	Increase of ALT but less than ULN		Increase of ALP or bilirubin but less than ULN		− 2	− 2
Not done or not interpretable					0	0
Score analysis (total score)	**Causal relationship:**		**Highly Probable**			> 8
			Probable		≥ 5	6 to 8
			Possible		3 to 4	3 to 5
			Unlikely		≤ 2	1 to 2
			Excluded			≤ 0

*CIOMS/RUCAM scale only

**"Information on "Alcohol or Pregnancy", "Concominant drugs" and "DIST" was not available in this study

DISCLOSURE

- The current study was supported in part by the Health and Labour Sciences Research grant from the Ministry of Health, Labour and Welfare in Japan.
- All authors have no personal or financial relationships relevant to this presentation existed during the past 12 months/during the conduct of the study.

BACKGROUND

- A standardized detection method for drug-induced liver injury (DILI) using medical information databases (MIDs) has not yet been established because of the complexity of diagnosis.
- As a diagnostic criterion for DILI, the Digestive Disease Week Japan 2004 (DDW-J) scale[1)], which was modified based on the international CIOMS/RUCAM scale[2)]

OBJECTIVES

We aimed to develop a DILI detection algorithm using MIDs, based on a Japanese clinical diagnostic criteria for DILI (DDW-J), and to examine its consistency with the international scale (CIOMS/RUCAM) and the applicability for assessment of potential risk factors.

RESULTS

1. DILI detection by DDW-J algorithm and comparison with CIOMS/RUCAM algorithm in Hamamatsu population (Fig. 1)

The DDW-J and CIOMS/RUCAM algorithms were equivalent for identifying the DILI cases, indicating the utility of our DILI detection method using MIDs.

2. Application of DDW-J algorithm to two MIDs (Table 2)

The DDW-J algorithm was applied to another MID, MDV population. Similarity in DILI incidences among four study drugs were observed between Hamamatsu and MDV populations.

3. Potential risk factors of DILI by antibiotics (Table 3)

Male showed a significantly higher risk for DILI after antibiotic treatments in both MID populations

A longer treatment, especially with CM and LX, showed a trend toward to higher risk of DILI.

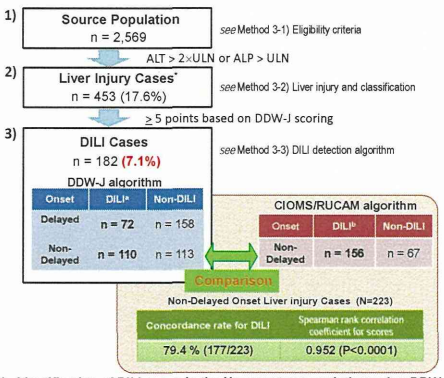

Fig. 1. Identification of DILI cases in the Hamamatsu population using DDW-J algorithm and comparison with CIOMS/RUCAM algorithm.

[a]Defined as a total score ≥ 5 in the DDW-J algorithm.

Table 2. DILI incidences after treatment with antibiotics in Hamamatsu and MDV populations

Drug	Hamamatsu (n=2,569)				MDV (n=3,856)			
	DILI (n)	Non-DILI (n)	Total (n)	DILI incidence (%)	DILI (n)	Non-DILI (n)	Total (n)	DILI incidence (%)
All drugs	182	2,387	2,569	7.1	237	3,619	3,856	6.1
CM	30	494	524	5.7	36	809	845	4.3
AM	17	160	177	9.6	43	422	465	9.2
LV	106	1,445	1,551	6.8	148	2,293	2,441	6.1
MX	29	288	317	9.1	10	95	105	9.5

CM: Clarithromycin , AM: azithromycin, LX: levofloxacin, MX: moxifloxacin

Table 3. Potential risk factors of DILI after treatment with antibiotics in Hamamatsu and MDV populations

Characteristics	Hamamatsu (n=2,569)				MDV (n=3,856)			
	DILI / non-DILI (%)	OR[a]	95% CI	P value	DILI / non-DILI (%)	OR[a]	95% CI	P value
Age ≥ 55	79.7 / 70.8	1.49	1.02–2.17	0.0371	73.8 / 75.4	0.85	0.63-1.16	0.3052
Male	63.7 / 53.2	1.44	1.05–1.98	0.0237	56.5 / 49.5	1.32	1.01-1.72	0.0409
Inpatient	40.1 / 31.9	1.38	1.01–1.90	0.0452	45.1 / 39.4	1.30	0.99-1.72	0.0624
Diabetes mellitus	8.8 / 9.3	0.81	0.47–1.38	0.4316	13.1 / 12.8	0.90	0.60-1.36	0.6225
High dose[b]	3.8 / 1.9	1.83	0.81–4.16	0.1473	5.1 / 3.5	1.34	0.73-2.48	0.3436
Long treatment[c]	35.2 / 32.2	1.14	0.83–1.57	0.4225	33.3 / 25.6	1.46	1.10-1.94	0.0082
CM: Days ≥ 8	46.7 / 40.7	1.19	0.56-2.52	0.6531	61.1 / 35.4	3.18	1.59-6.37	0.0011
CM: Days ≥ 28	33.3 / 18.8	2.08	0.91-4.80	0.0846	33.3 / 14.2	2.97	1.43-6.15	0.0034
LX: Days ≥ 8	34.0 / 31.6	1.15	0.75-1.76	0.5273	35.1 / 25.8	1.57	1.10-2.23	0.0122

CI: confidence interval, DILI: defined as DDW-J score ≥5

[a] Adjusted for age (≥55 years), gender, in/outpatient status, diabetes mellitus, treatment duration, and high dose.

[b] Higher than usual approved dose.

[c] ≥8 days for clarithromycin(CM), levofloxacin(LX), and moxifloxacin(MX), and ≥4 days for azithromycin (AM).

CONCLUSIONS [3)]

- **We have developed a DILI detection algorithm using MID based on the Japanese DILI diagnostic scale and showed its applicability for quantitative assessment of DILI and its potential risk factors.**
- **This study supports the utility of MID-based research for improving pharmacovigilance.**

1) Tajiri K, Shimizu Y. Practical guidelines for diagnosis and early management of drug-induced liver injury. *World J Gastroenterol* 2008; 14: 6774–6785.
2) Danan G, et al., A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. *J Clin Epidemiol* 1993; 46:1323–1330.
3) Hanatani T *et al.* A detection algorithm for drug-induced liver injury in medical information databases using the Japanese diagnostic scale and its comparison with the Council for International Organizations of Medical Sciences/the Roussel Uclaf Causality Assessment Method scale. *Pharmacoepidemiol Drug Saf.* 2014;23:984-8.

医療情報データベースを活用した副作用としての無顆粒球症の検出に関する研究

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[3]浜松医科大学医学部附属病院薬剤部

Introduction

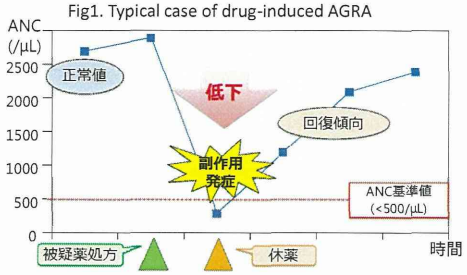
医薬品の市販後の安全性評価は副作用の自発報告に大きく依存している。しかし、客観性に乏しい場合もあり、また服用患者数の情報がないことから発生頻度の把握が困難である。そこで電子医療情報データの利活用により、薬剤性副作用の発症を判別する検索式を構築することで、簡便に副作用症例の客観的な検出と発生頻度を得られる可能性がある。本研究では重篤副作用の一つである無顆粒球症に注目し、検索式の確立を試みた。

Methods

データベース：浜松医科大学医学部附属病院が有する臨床情報検索システム「D*D」（処方、検査値、疾病データを含む）
対象患者：1996年1月～2012年2月までに同病院において被疑薬を処方された全患者
対象副作用：無顆粒球症(AGRA)
被疑薬：Ticlopidine, Thiamazole(MMI), Propyltiouracil(PTU), Salazosulfapyridine(SASP), Mesalazine(5-ASA), Clozapine, Chlorpromazine, Mianserin
解析ソフト：SAS9.4
確定診断：真の無顆粒球症患者を同定するため、カルテ調査を行い専門医による確定診断を実施する。

本研究は名古屋市立大学医学部及び浜松医科大学の倫理審査委員会の承認を得て実施した。

Fig1. Typical case of drug-induced AGRA



Results

1. 検索アルゴリズム組み入れ患者の選定

「D*D」から被疑薬服用前後6ヶ月以内に白血球数(WBC)、分葉核球数(SEG)、桿状核球数(STAB)、ヘモグロビン(Hb)、血小板数(PLT)のいずれかの検査が行われた患者を抽出(N=4,921)

- 除外基準1：初回投与後90日以内にANC算出不可※1 (N=2,620)
- 除外基準2：発症（ANC<500/μL）30日以内に抗がん剤の投与有り (N=45)

Ticlopidine(N=980), MMI(N=456), PTU(N=138), SASP(N=382), 5-ASA(N=144), Clozapine(N=1), Chlorpromazine(N=175), Mianserin(N=141), **Total(N=2,256)**

※1　ANC：Absolute Neutrophil Count
ANC＝(SEG＋STAB)×WBC

2. 検索アルゴリズムの構築

(0)無顆粒球症の定義	ANC<500/μLを記録
(1)好発時期＆被疑薬の限定	被疑薬初回投与90日以内かつ最終投与日（最終処方日＋投与日数）から21日以内にANC<500/μLを記録
(2)類似疾患の除外	ANC<500/μL時にHb≧(10 or 9)g/dL＆PLT≧10万/μLを記録
(3)休薬	無顆粒球症状態後30日以内に被疑薬再投与がみられない
(4)回復傾向	無顆粒球症状態後30日以内にANC≧500/μLを記録し、その後ANC≧500/μLを維持

3. アルゴリズムで抽出された疑い症例

Table1. Characteristics of suspected AGRA patients in case of Hb≧10g/dL (N=3)

No.	Gender	Age	ANC(/μL)	PLT(10^4/μL)	Hb(g/dL)	Suspected Drug
1	Female	34	322	24.3	11.5	MMI PTU
2	Female	49	455	21.3	11.3	MMI PTU
3	Male	51	0	41.7	15.8	MMI

Table2. Characteristics of suspected AGRA patients in case of Hb≧9g/dL(N=5)

No.	Gender	Age	ANC(/μL)	PLT(10^4/μL)	Hb(g/dL)	Suspected Drug
1	Female	34	322	24.3	11.5	MMI PTU
2	Female	49	455	21.3	11.3	MMI PTU
3	Male	51	0	41.7	15.8	MMI
4	Female	73	140	33.6	9.3	Ticro
5	Female	23	9	38.4	9.9	SASP

4. 検索アルゴリズムの性能評価

Table3. Evaluation of the algorithm in case of Hb≧10g/dL

アルゴリズム	薬剤性副作用	副作用なし	計
陽性	3	0	3
陰性	4	2,249	2,253
計	7	2,249	2,256

PPV =1.000(3/3)
NPV =0.998(2249/2253)
感度 =0.429(3/7)
特異度 =1.000(2249/2249)

Table4. Evaluation of the algorithm in case of Hb≧9g/dL

アルゴリズム	薬剤性副作用	副作用なし	計
陽性	5	0	5
陰性	2	2,249	2,251
計	7	2,249	2,256

PPV =1.000(5/5)
NPV =0.999(2249/2251)
感度 =0.714(5/7)
特異度 =1.000(2249/2249)

処方データと検査値データのみから、感度70%、特異度100%のアルゴリズムを作成することができた。

Discussion

- 無顆粒球症の定義は「ANC<500/μL」であるが、HbやPLT、投与期間、最終投与日から発症までの期間が検索式の感度・特異度に影響を与えると考えられる。実際にHbの基準値を変えることで検出された疑い症例が3人から5人に増加した。
- 今後は、今回作成したアルゴリズムを他の大学病院のDBに適応し、検証的解析を行う。
- 本研究では1施設のデータを基にして、検査値、期間等の閾値を設定した。従って、規模や機能の異なる他施設のデータを用いる場合には、閾値を再検討する必要がある。

Conclusion

- 今回用いた検索アルゴリズムについて、SASプログラミング化が可能であり、データフォーマットを統一することで、自動的、簡便に疑い症例を抽出することが可能となった。
- アルゴリズム内の基準値を変動させることで、最適なカットオフ値をもつ検索式構築のための条件を設定することが可能となった。

第24回日本医療薬学会年会
利益相反の開示
筆頭発表者名：山田 健人
私は今回の演題に関連して、開示すべき利益相反はありません。