バリデーション関連情報の確認
Validity of Pharmacoepidemiologic Drug and Diagnosis Dataより
（Pharmacoepidemiology, Part V Chapter 41）

日本における傷病名を中心とするレセプト情報から得られる指標のバリデーションに関するタスクフォース

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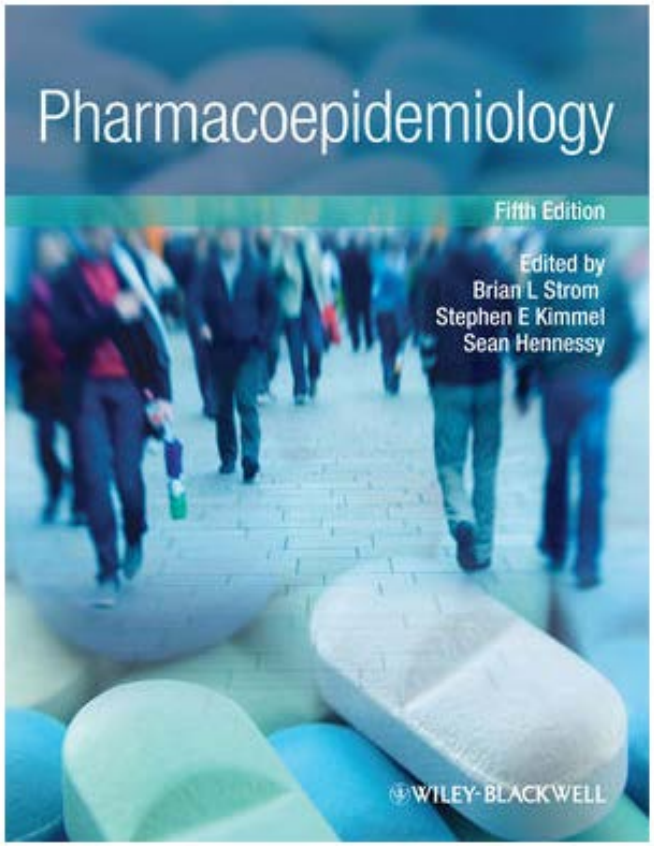
Pharmacoepidemiology, 5th Edition



PART I

Introduction

PART II

The Role of Pharmacoepidemiology in Different Sectors

PART III

Sources of Data for Pharmacoepidemiologic Studies

PART IV

Selected Special Applications of Pharmacoepidemiology

(Chapter 41)

Validity of Pharmacoepidemiologic Drug and Diagnosis Data

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PART V

Selected Special Methodologic Issues in Pharmacoepidemiology

PART VI

Conclusion

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Validity of Pharmacoepidemiologic Drug and Diagnosis Data

1. Introduction
2. Clinical problems to be addressed by pharmacoepidemiologic research
3. Methodologic problems to be solved by pharmacoepidemiologic research
4. Currently available solutions

疫学者はデータの統計解析に魅了され、研究の結論の正確さ（veracity）の土台となる、生データの妥当性（validity）への注意が乏しい。
本書では、薬剤疫学研究で関連が注目され、また重要な潜在的な交絡因子の多くを構成する、薬剤曝露と疾患発生に関するデータの妥当性に触れる。

Methodologic problems to be solved by pharmacoepidemiologic research

- 妥当性（validity、同義語：accuracy）
  - 指標：感度（sensitivity）、特異度（specificity）

妥当性評価には“gold standard”が必要
- gold standard：他と比較し明らかに優れている方法/情報源
- “alloyed gold standard”：不完全なgold standard

⇔調和度（concordance）、一致度（agreement）
・gold standardが無いなかでの方法/情報源の比較

- 信頼性（reliability）
  - 指標：一致度とκ係数（偶然一致を補正した一致度）

Methodologic problems to be solved by pharmacoepidemiologic research

- 妥当性の指標：Gold Standard（真値）が分母
  - 感度：注目した特徴を有する人を正しく同定した割合
  - 特異度：注目した特徴を有さない人を正しく同定した割合

> ✓ いずれが重要な妥当性の尺度かは研究設定により変わる
> ✓ これらの指標の絶対値はあまり意味が無く、究極の基準は効果の測定に影響するバイアスの程度（次スライド参照）

⇔的中度は正確には妥当性の指標では無い。その方法/情報源の性能（Performance）の尺度：観察値が分母

- 陽性的中度（PPV）：注目した特徴があると観察された人が実際にその特徴を有している割合
- 陰性的中度（NPV）：注目した特徴がないと観察された人が実際にその特徴を有していない割合

ただ、バリデーションスタディでは、上記4指標を算出できるようデザインすることが理想的

Methodologic problems to be solved by pharmacoepidemiologic research

例）各研究で異なる「曝露の割合」の影響により、case-control研究の結果（オッズ比）が変わる

- 真のオッズ比(OR)：3.0
- 曝露の測定への妥当性尺度：
  - 感度：（ケース）0.9、（コントロール）0.8
  - 特異度：（ケース）0.95、（コントロール）0.99

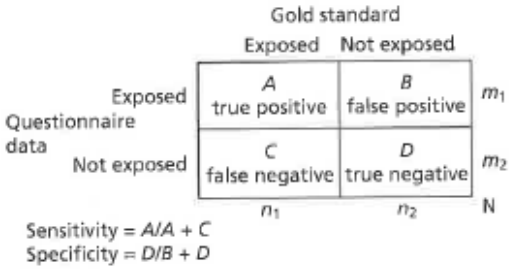

Figure 41.1 Formulas for calculating sensitivity and specificity.

ソース集団の曝露割合 = 10%			
真）			
	Case	Control	
曝露	60	200	OR =3.0
非曝露	180	1800	
→			
	Case	Control	
曝露	63	178	OR =3.6
非曝露	177	1822	

ソース集団の曝露割合 = 90%			
真）			
	Case	Control	
曝露	540	1800	OR =3.0
非曝露	20	200	
→			
	Case	Control	
曝露	487	1442	OR =2.6
非曝露	73	558	

Currently available solutions

-validity of pharmacoepidemiologic drug and diagnosis data from computerized databases containing administrative or electronic medical record data-

- データベースの選択において極めて重要な要素
  - 完全性（Completeness）＊
    - データベースでカバーされる集団にて発生した「注目している曝露/事象」のうち、実際にデータベースで確認できる割合

      （＊別の章にて、感度と同等のものと説明されている）
  - 妥当性（Validity）
    - 前述の通り
- これらは、administrative dataと他のdata（ex. medical records, administrative or billing records, pharmacy dispensings, or procedure logs）との比較により確認される。
  - 比較する側のデータの限界にも留意する必要がある

Currently available solutions

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Administrative dataのvalidation study

1. 有意義な患者数を選択
   - 患者数は統計学的に妥当なものでなければならないが、データの可用性、費用、労務への考慮は理解できる
2. 変数を抽出
   - コホート選択、曝露、アウトカムなどを決定するために必要な変数を選択する
3. 一致の程度を測定
4. 強み・限界を考察
   - 研究主題に答えられるものか、そのデータの妥当性・完全性を確認する

Currently available solutions

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- Drug data in administrative or medical record databases
  - 請求データは、正確に完全に曝露情報を表していると思いがちだが、未請求処方（全請求の2%程が該当）、アドヒアランス、OTC医薬品など考慮すべき点はあり、新たな医薬品曝露やデータベースを使用するときは、妥当性を検討すべきである。
  - 以前、評価されたデータであっても、医療行為の変化等に伴い、さらなる妥当性評価が必要（アウトカムも同様）。

Currently available solutions

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- Diagnosis and hospitalizations in administrative databases
  - Drug dataと異なり、妥当性がよく懸念となる
    - 外来患者の診断データは特に不確かさが高い
    - ICD等による系統誤差
  - 妥当性の評価
    - 診療録との比較が多い
    - 陽性的中度（PPV）の算出が多く、感度・特異度を算出するものは多くは無い

Currently available solutions

-validity of pharmacoepidemiologic drug and diagnosis data from computerized databases containing administrative or electronic medical record data-

- 心筋梗塞

Table 41.3 Validation of MI and GI events in studies using administrative data to evaluate harms of NSAID exposure

Author	Dataset	Study sample size	Study aim	Comparison data source	Conditions	Findings
Brophy, 2007[148]	Computerized health databases of Quebec, Canada	n = 234 MI survivors	To determine whether a history of MI modified the risk of acute MI associated with the use of various NSAIDs	Previous validation of MI claims;[149] no validation of NSAID use	MI: hospitalization with ICD-9 code 410, considered fatal if person died within 30 days of admission	PPV = 0.96 (95% CI: 0.94–0.98)
Varas-Lorenzo, 2009[149]	Saskatchewan Health	n = 200	To evaluate risk of fatal and non-fatal acute MI with NSAID use	Medical records	ICD-9 code 410–414, 427.5, 798 ICD-10 code I20-I22, I23.3, I24-I25, I46, R96.0, R96.1, R98 Abstraction items included available information on cardiac symptoms; copies of available electrocardiograms recorded during the first 72 hours after hospital admission and the last one before hospital discharge; serum biomarkers levels: troponins, CPK-MB, or CPK measured within first 72 hours and compared with later measures; necropsy and other cardiac diagnostic test findings. Based on abstracted information two cardiologists classified events as definite or probable/possible (either fatal or non-fatal) according to adapted standardized criteria recently adopted by American Heart Association/European Society of Cardiology Classification of exposure to NSAIDs was based on the days between the index date and the end of supply of the most recent dispensing before the index date	PPV for ICD-9 code 410 = 0.95 (95% CI: 0.91–0.98) PPV for ICD-9 code 411 for intermediate coronary syndrome = 0.73 (95% CI: 0.70–0.77) PPV for ICD-9 code 411 for AMI = 0.09 (95% CI: 0.07–0.11)

Currently available solutions

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- 心筋梗塞

Author	Dataset	Study sample size	Study aim	Comparison data source	Conditions	Findings
Wahl, 2010[150]	HealthCore Integrated Research Database	n = 200 charts per outcome	To validate administrative claims codes with medical chart review for MI, ischemic stroke, and severe upper gastrointestinal (UGI) bleed events in a large, commercially-insured US population	Medical charts	MI: ICD-9 code 410.xx excluding 410.x2 and a length of stay (LOS) between 3 and 180 days, or death if LOS is <3 days Severe UGI bleed events were defined as a hospitalization for either UGI hemorrhage or peptic ulcer disease, including perforation. In the claims data, this was defined as ICD-9 codes 531.x, 532.x, 533.x, 534.x, 578.0, 578.1, 578.9, or a physician service code for GI hemorrhage (CPT code 43255 or ICD-9 procedure code 44.4x).	Overall: PPV for MI = 88.4% (177/200; 95% CI: 83.2–92.5%) PPV for ischemic stroke = 87.4% (175/200; 95% CI: 82.0–91.7%) PPV for severe UGI bleed = 56.5% (109/193; 95% CI: 49.2–63.6%) Among those taking NSAIDs: PPV for MI = 92.3% (97/105; 95% CI: 85.4–96.6%) PPV for ischemic stroke = 78.9% (57/72; 95% CI: 67.6–87.7%) PPV for severe UGI bleed = 57.9% (70/121; 95% CI: 48.5–66.8%)

- 患者背景によりコード化に差異がある可能性
- 医薬品（曝露）とアウトカムのペアで妥当性を検証すべき？

Currently available solutions

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- 消化管出血

Table 41.3 Validation of MI and GI events in studies using administrative data to evaluate harms of NSAID exposure

Author	Dataset	Study sample size	Study aim	Comparison data source	Conditions	Findings
Abraham, 2006[154]	VA	N = 906 ICD-9-CM codes and CPT procedure codes in patient treatment and outpatient care databases indicating upper gastrointestinal events (n = 606) Controls (n = 300)	To validate Veterans Affairs (VA) administrative data for the diagnosis of NSAID-related upper gastrointestinal events (UGIE) and to develop a diagnostic algorithm	Medical records	Case definition for UGIE was any of the following: Gastric ulcer 531.0, 531.1, 531.2, 531.3, 531.4, 531.5, 531.6, 531.7, 531.9 Duodenal ulcer 532.0. 532.1, 532.2, 532.3, 532.4, 532.5, 532.6, 532.7, 532.9 Peptic ulcer 533.0, 533.1, 533.2, 533.3, 533.4, 533.5, 533.6, 533.7, 533.9 Gastrojejunal ulcer with perforation 534.0, 534.1, 534.2, 534.3, 534.4, 534.5, 534.6, 534.7, 534.9 Gastrointestinal hemorrhage 578.0, 578.1, 578.9	Only ICD-9 codes for UGIE: Sensitivity: 100% Specificity: 96% PPV: 27% NPV: 100% ICD-9 and CPT for UGIE: Sensitivity: 82% Specificity: 100% PPV: 51% NPV: 99% ICD-9 and CPT algorithm for UGIE: Sensitivity: 66% Specificity: 88% PPV: 67% NPV: 88% Algorithm validated in additional 44 patients, PPV among NSAID users: 80%

Currently available solutions

-validity of pharmacoepidemiologic drug and diagnosis data from computerized databases containing administrative or electronic medical record data-

- 消化管出血

Author	Dataset	Study sample size	Study aim	Comparison data source	Conditions	Findings
Castellsague, 2009[155]	Saskatchewan Health	Specific codes: n = 38 (10% sample) Non-specific codes: n = 742 (all potential cases)	To estimate the risk of upper gastrointestinal complications associated with use of cyclooxygenase-2 (COX-2) selective (celecoxib and rofecoxib) and individual non-selective non-steroidal anti-inflammatory drugs compared with non-use of these drugs	Medical records	Upper gastrointestinal complications: ICD-9 codes 531.0–531.2, 531.4–531.6, 532.0–532.2, 532.4–532.6, 533.0–533.2, 533.4–533.6, 534.0–534.2, 534.4–534.6, 569.3, 569.4, 569.8, 578	Previous research: PPV for site- and lesion-specific peptic ulcer disease codes in Saskatchewan =91% PPV for non-specific codes = 68%. This study: Specific PPV = 92% Non-specific code PPV (ranged across codes) = 60% for unspecified hemorrhage, 4% for hemorrhage of rectum/anus
van Staa, 2009[158]	GPRD	n = 96	To evaluate the external validity of published cost-effectiveness studies by comparing the data used in these studies to observational data from actual clinical practice and whether these studies should have been used to inform prescribing policies Selective Cox-2 inhibitors (coxibs) and upper GI events were used as an example	Medical records	Upper GI events: ICD-10 codes K25–K29 NSAIDS: any prescription in GPRD	PPV = (95/96) = 99.0%

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– 複数のデータベースにおける、同じアルゴリズムを用いた妥当性（感度、特異度）の結果が、手助けとなる