

Validation of Expert Opinion in Identifying Comorbidities Associated with Atopic Dermatitis/Eczema

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Abstract

Background: The use of expert opinion is widespread in economic studies of healthcare utilisation; however, few studies have attempted to assess the validity of assumptions derived from such sources.

Objective: To examine the use of such expert opinion in determining comorbidities associated with atopic dermatitis/eczema (AD/E), which were assessed as part of a recent third-party payer cost-of-illness study.

Design: To identify the disease-related comorbidities that would represent costs associated with AD/E, physicians on an expert panel were asked individually and then collectively to group all International Classification of Diseases, 9th Edition–Clinical Modification (ICD-9-CM) diagnosis codes as ‘most likely’, ‘possibly’ or ‘definitely not’ related to the costs of identifying and treating patients with AD/E. Claims representing \$US464 million in payer reimbursements from nearly 125 000 patients with AD/E were identified within two separate claims databases (1997 values). Over 850 ICD-9-CM diagnosis codes were identified in the first-listed position from these claims. For each group of ‘most likely’, ‘possibly’

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and 'definitely not' related diagnosis codes, prevalence rates were compared within AD/E and non-AD/E populations from the two historical payer claims databases. Adjusted and non-adjusted odds ratios were calculated by comparing prevalence rates between AD/E and non-AD/E patients in the same payer population.

Results: The mean prevalence rate of any diagnosis code in the AD/E population was $0.65 \pm 1.82\%$ (SD) with a mean odds ratio of 1.81 ± 0.96 . Comorbidities considered by the expert panel 'most likely' to be associated with AD/E had higher prevalence rates ($3.28 \pm 3.63\%$) and odds ratios (2.14 ± 1.14). Comorbidities considered to be 'possibly' related to AD/E had prevalence rates and odds ratios of $3.01 \pm 5.06\%$ and 1.84 ± 0.82 , respectively. Comorbidities considered to be 'definitely not' related to AD/E had the lowest prevalence rates ($0.45 \pm 1.09\%$) and odds ratios (1.80 ± 0.97).

Conclusions: Comparing the result of consensus panels with actual claims histories validated the use of expert opinion in determining comorbidities associated with AD/E. Expert opinion yielded valid results in terms of identifying comorbidities that manifested frequently and disproportionately in the AD/E population. Limited statistical measurements of comorbidities would have been less specific than expert opinion. Future cost-of-illness studies should consider alternative data sources and methodologies to enhance the validity and importance of expert opinion and to corroborate their findings.

Expert opinion is applied in clinical medicine and health services research to bridge the gap between existing knowledge and areas in which prior research is inadequate or non-existent.^[1-3] The use of expert opinion in health economics studies is widespread and applied to assist researchers in documenting the natural history of disease, treatment protocols and resource utilisation.^[4,5] Because expert opinion is subjective in nature, some have discounted its scientific validity.^[6] And when expert opinion is applied to economic studies, researchers increasingly have called for standards in its application and the reporting of techniques used.^[7]

Readers' abilities to understand and accept assumptions based on expert opinion may be affected by whether expert opinion can be validated with concrete observations. Regarding the use of expert opinion via the Delphi method to conduct research, Pill argued that "it should be possible to apply

Delphi in conjunction with a more concrete procedure which works backward from the real world".^[8] One way to address the performance of expert opinion is to compare results with actual observations. Unfortunately, economic research that employs expert opinion has not attempted to employ quantitative, fact-based knowledge to validate those assumptions.^[9-11]

Recently, Ellis et al. examined the direct medical costs associated with atopic dermatitis/eczema (AD/E) based on third-party payer claims histories.^[12] In addition to identifying patients and claims based on the International Classification of Diseases, 9th Edition—Clinical Modification (ICD-9-CM) diagnosis codes specific to atopic dermatitis and eczema, other claims were included in the cost analysis to account for related comorbidities and medical treatments. As with other cost-of-illness studies, physician expert opinion was sought to

identify comorbidities or other medical therapies 'most likely' and 'possibly' attributable to the underlying disease. The inclusion of comorbidities greatly increased the burden of illness associated with other chronic diseases such as allergic rhinoconjunctivitis, sinusitis and asthma.^[13-17]

Expert opinion also played a considerable role in quantifying the total cost of AD/E within the Ellis study.^[12] The addition of related comorbidities and prescription drugs increased the total cost of disease up to 9-fold within Medicaid patient populations (mean cost of \$US120 per patient for AD/E compared with \$US1010 per patient for related comorbidities and drugs [1997 values]).

The purpose of this study was to validate the use of expert opinion for the identification of comorbidities within defined patient populations as applied to health services and economic research. We assessed whether physician expert opinion is reliable in identifying comorbidities associated with AD/E to the extent that they would have an impact on the overall cost of illness. In the absence of established standards to validate the reliability of expert opinion, we elected to use comorbidity prevalence rates as our 'unit' of measurement – both in terms of the overall prevalence rate of any given comorbidity, and the relative prevalence rate of a given comorbidity in the AD/E population compared with a control group.

Methods

This study sought to validate expert opinion used in a previously published cost-of-illness study. First, we review the methodology employed in the original cost-of-illness study. Second, we discuss the methodology for the validation of the expert opinion.

Cost-of-Illness Study

AD/E is a highly pruritic, recurring inflammatory skin disease that develops in early childhood. Dis-

ease prevalence has increased steadily in recent years, and is estimated to affect over 10% of infants and children.^[18]

Data Sources

Ellis et al. analysed claims data from private insurance and state Medicaid claims databases from 1996 and 1997 to estimate costs associated with AD/E. All claims submitted to each respective third-party payer for all beneficiaries during that period of time were included in the claims databases.^[12]

Patient Population

Patients were considered to have AD/E if they had at least one claim in 1997 with a primary or secondary listing of one of three ICD-9-CM diagnosis codes: 691.8, other atopic dermatitis and related conditions; 692.9, contact dermatitis and other eczema unspecified cause (including eczema not otherwise specified); or 373.3, dermatoses of eyelid. Patients who did not meet these criteria were evaluated as part of a 'control' group for comparisons of disease prevalence with the AD/E group.

Identifying Disease-Related Comorbidities

Third-party payer expenditures that could be linked directly to any given disease often go unreported and may result in the underestimation of the total cost of illness. Previous reports have estimated that approximately 80% of patients with atopic dermatitis have IgE reactivity (elevated total or specific serum IgE levels and/or immediate skin test responses) or clinical asthma and allergic rhinoconjunctivitis. The altered immune response in the skin of patients leads to xerosis, itching, rubbing, scratching, excoriation, lichenification, weeping and secondary infections. Other physiological and psychological comorbidities are commonly reported for AD/E.^[18,19]

Therefore, to provide a more comprehensive assessment of the cost-of-illness for AD/E, a panel of clinician authors (seven dermatologists and one allergist/immunologist) was formed to define the

comorbidities most commonly associated with AD/E.^[12] Panellists from different geographical regions were identified based on research, publications and clinical experience in AD/E. The expert panel identified prospective comorbidities that were clinically relevant. The panel was blinded to resource utilisation patterns and economic consequences. The process of identifying comorbidities included both Delphi and expert panel techniques involving assessments by individuals and in group forums.^[7]

Individual panellists were given lists of all existing ICD-9-CM diagnosis codes. They were asked individually through a mail survey to determine the diagnosis codes 'most likely' and 'possibly' related to the costs of diagnosing and managing patients with AD/E. All other diagnosis codes were considered 'definitely not' related to AD/E. Data were compiled by an independent researcher and reported back to the group collectively for discussion and consolidation. To refine the assignments and resolve further differences in the assignment of diagnosis codes, panel members reviewed the categorisations collectively a second time. All categorisations of comorbidities were done with panellists unaware of the frequency of claims and expenditures.

The private insurance and state Medicaid claims databases used for the analysis included over 3 million beneficiaries. Nearly 125 000 patients with AD/E were identified based on the three AD/E diagnosis codes. Claims for AD/E and non-AD/E patients were analysed and found to contain over 850 first-listed diagnosis codes (based on ICD-9-CM three-digit classifications) which were each grouped according to the categories set previously by the expert panel. Costs for 'most likely' and 'possibly' related diagnosis codes were compared between the AD/E population and the non-AD/E population (used as the control group).

The prevalence of individual diagnosis codes within the AD/E population was compared with the

control group to calculate non-adjusted and age-adjusted odds ratios for each diagnosis code. Further comparisons were performed to determine whether per patient expenditures for 'most likely' and 'possibly' related diagnosis codes were greater in the AD/E population compared with controls. Severity of illness, which would represent a potentially important confounder for comorbidity prevalence and costs, was not available through the claims databases, and thus not accounted for within the study. Other variables such as gender and payer type did not have a significant impact on comorbidity prevalence.

Validation of Expert Opinion

Expert opinion was sought in the cost-of-illness study^[12] to identify comorbidities associated with a chronic, recurrent illness (namely AD/E) because other sources of evidence were not available.^[20] In order to validate the recommendations provided by the panel, the same claims databases used in the original study were compiled. This study analysed the validity of diagnosis code assignment because there was a large sample to work with (over 850 diagnosis codes) and costs associated with diagnosis codes represented over 75% of the expenditures included in the cost-of-illness study.

Criteria used to validate the consensus opinions were defined as follows:

1. *Within the AD/E population.* The prevalence rate for each diagnosis code that appeared in the first-listed position on claims was calculated. Next, mean prevalence rates were calculated for each of the three diagnosis code groupings ('most likely', 'possibly' and 'definitely not' related to AD/E). Because physicians could be expected to identify common comorbidities that are highly prevalent in the disease population more readily than those that are not common, it was thought that the absolute prevalence rate of conditions identified as 'most likely' and 'possibly' related to AD/E as a whole might be higher

Table I. Mean prevalence and odds ratios for diagnosis codes by category

	Mean prevalence ^a (%)	SD (%)	Mean odds ratio ^b	SD
All ICD-9-CM diagnosis codes (n = 861)	0.65	1.82	1.81	0.96
Most likely related codes (n = 15)	3.28	3.63	2.14	1.14
Possibly related codes (n = 51)	3.01	5.06	1.84	0.82
Definitely not related codes (n = 795)	0.45	1.09	1.80	0.97

a For comparison of mean prevalence between 'most likely' and 'definitely not' related codes, and between 'possibly' and 'definitely not' related codes, $p < 0.01$ for each; differences between 'most likely' and 'possibly' related codes were not statistically significant.

b Comparisons across all groups showed no statistically significant differences.

ICD-9-CM = International Classification of Diseases, 9th Edition—Clinical Modification.

(and certainly not lower) than those that were 'definitely not' related. Therefore, comorbidities considered by the panel to be 'most likely' and 'possibly' related were compared within the AD/E population with prevalence rates for diagnosis codes considered 'definitely not' related.

2. *Compared with the control population.* If the comorbidities selected by expert opinion were indeed uniquely related to patients with AD/E, it follows that the prevalence rate of those conditions should be higher among patients with AD/E when compared with the control population. Subsequently, odds ratios were used to assess whether the clinicians' frame of reference could account in large part for the selection of specific diseases as being related to AD/E. Unadjusted and age-adjusted odds ratios were calculated by comparing prevalence rates in the AD/E population with those in the control population for all ICD-9-CM diagnosis codes found in the claims databases. Mean odds ratios for the 'most likely' and 'possibly' related diagnosis codes were compared with those corresponding to the 'definitely not' related codes. Unpaired student t-tests were used to compare means at a 0.05 level of significance for both prevalence and odds ratio comparisons. All statistical analyses were conducted using SPSS® statistical software version 10.0.^[21]

Results

The mean prevalence rate for all potential comorbidities was $0.65 \pm 1.82\%$ (SD) with a mean odds ratio of 1.81 ± 0.96 (table I). Age-adjusted and non-

adjusted odds ratios were similar (data not shown). A log-adjusted scatter plot of prevalence rates and odds ratios revealed a bell-curve shaped distribution (figure 1).

Comorbidities considered by the expert panel 'most likely' to be associated with AD/E had the highest mean prevalence rate ($3.28 \pm 3.63\%$) and odds ratio (2.14 ± 1.14). Comorbid conditions considered to be 'possibly' related to AD/E had a mean prevalence rate of $3.01 \pm 5.06\%$ and odds ratio of 1.84 ± 0.82 . Diagnosis codes categorised as 'definitely not' related to AD/E had the lowest mean prevalence rate ($0.45 \pm 1.09\%$) and odds ratio (1.80 ± 0.97) [table I]. A scatter plot displays the distribution of all the diagnosis codes analysed within this study (figure 2). Statistically, mean prevalence rates for codes 'most likely' and 'possibly' related to AD/E were significantly higher when each one individually was compared with 'definitely not' related codes ($p < 0.01$ for both groups). No statistical differences in prevalence rates were found between 'most likely' and 'possibly' related codes. Differences in odds ratios across all groups were not statistically significant (table I).

Discussion

Various sources of information are used to evaluate costs of illness including published literature, fee schedules, hospital records and administrative and epidemiological databases. The lack of standards and methods applied to cost-of-illness studies has resulted in criticisms regarding the usefulness of

such studies.^[22] Other studies have used physician input in conjunction with actual utilisation data to draw conclusions; however, no study has attempted to validate the methodology of using a physician panel either to estimate directly or indirectly disease costs and resource utilisation.^[9]

The cost-of-illness study conducted by Ellis et al. relied on large, administrative claims databases to estimate the cost of illness for AD/E.^[12] The authors relied on healthcare claims data from two different third-party payers including data on over 3 million beneficiaries to identify a cohort of patients with AD/E and the annual costs of medical care they received. Medical costs directly attributable to AD/E were obtained by aggregating claims with disease-specific ICD-9-CM diagnosis codes. Since AD/E is a chronic disease associated with other underlying diseases and comorbidities, expert opinion was sought and used to identify other possible comorbidities related to AD/E in an attempt to estimate the total cost of illness.

This study represents one of the first attempts to validate the utility of expert opinion as applied within the context of a cost-of-illness study. Conceptually, potential comorbid conditions of a particular disease, in this case AD/E, can be thought of as

falling into one of four descriptive quadrants: (i) low prevalence, low odds ratio; (ii) low prevalence, high odds ratio; (iii) high prevalence, low odds ratio; and (iv) high prevalence, high odds ratio. This last category is arguably the most useful in estimating costs associated with comorbidities, because the greatest proportion of the disease population will be affected by conditions in this quadrant. The current study found that expert opinion was selective in identifying comorbidities that were of both: (i) high prevalence compared with other diagnoses within the AD/E population, and (ii) greater frequency in the AD/E population than in a control population.

It is interesting to note that the prevalence rates for all diagnosis codes were generally low (0.65% across all diagnosis codes), and associated with large standard deviations (1.82% across all diagnosis codes). However, the prevalence rates for 'most likely' and 'possibly' related diagnosis codes were 7-fold higher than prevalence rates for conditions considered not to be related. The high standard deviations surrounding these codes were expected and should not be of great concern because they are likely, due in part to the small number of codes assigned to each category as well as the natural prevalence rates surrounding known disease states,

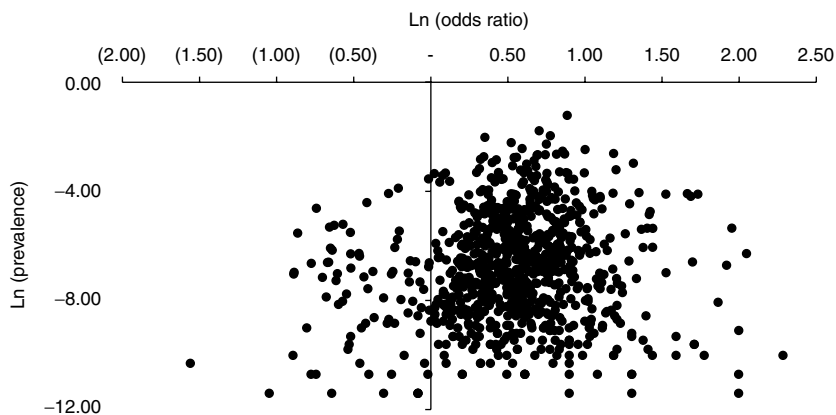


Fig. 1. Scatter plot of the natural log of prevalence and odds ratios for all first-listed diagnosis codes recorded for patients with atopic dermatitis/eczema. The natural log (Ln) of odds ratios and prevalence rates for over 850 diagnoses appearing in atopic dermatitis/eczema patient claims was plotted along x and y axes, respectively. The scatter plot shows a bell curve distribution skewed towards a higher odds ratio (mean 1.81, Ln[1.81] = 0.59).

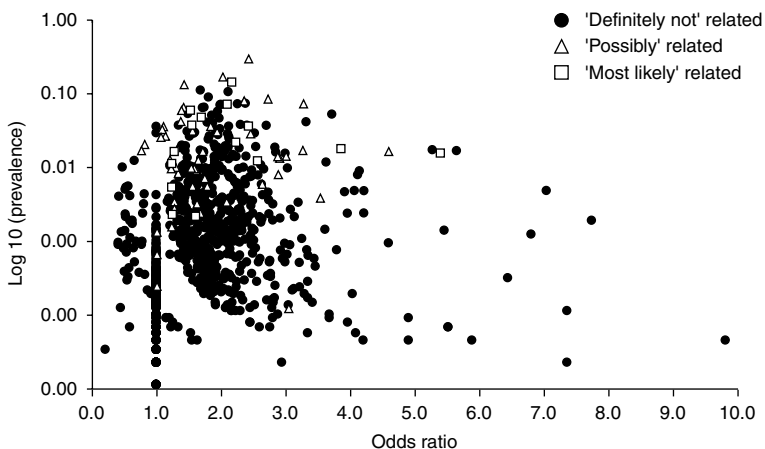


Fig. 2. Scatter plot of diagnosis codes for patients with atopic dermatitis/eczema by prevalence and odds ratio categorised by expert opinion. The odds ratio and prevalence rates of diagnoses appearing in atopic dermatitis/eczema patient claims were plotted along x and y (log scale) axes, respectively. For visual clarity, odds ratios where the 95% CIs included 1.00 were plotted as 1.00; all other plotted odds ratios have 95% CIs that do not include 1.00. Diagnoses considered to be 'most likely' related are shown using squares; those considered to be 'possibly' related are shown using triangles; those considered 'definitely not' related are shown using circles. The scatter plot shows that diagnoses considered to be related to atopic dermatitis/eczema by expert opinion had generally higher prevalence rates and odds ratios.

ranging from the very common to the extremely rare.

Solely mathematical approaches in identifying AD/E comorbidities would not have yielded the same list of diagnoses compared with those generated through expert opinion. Diseases with the highest prevalence rates in the AD/E population were not universally categorised by the expert panel as 'most likely' related, although a strong relationship exists (table II). There were several other diagnoses with extremely high odds ratios that were not selected through expert opinion (e.g. toxic effect of metals, lichen planus/nitidus, maternal complications). Many of these appear to be of questionable rele-

vance due to low overall prevalence rates found in the AD/E population (table III). For the purposes of a cost-of-illness analysis, low prevalence rates would have minimised the impact of these diseases on overall costs. This comparison, nonetheless, suggests that expert opinion may be more sensitive and specific than mathematical approaches in identifying comorbidities, and reinforces the value of real-world clinical experience in correctly differentiating potentially related conditions from statistical outliers.

Odds ratios for all diseases within the AD/E population were generally greater than 1.00, with a mean of 1.81. Only 78 of over 850 diagnosis catego-

Table II. Most prevalent diagnosis codes found within atopic dermatitis/eczema patient claims

Description (ICD-9-CM code)	Prevalence rate (%)	Expert opinion category	Odds ratio rank ^a
Top 5 diagnoses by prevalence			
Acute upper respiratory infection (465)	30	Possibly	149
Otitis media (382)	17	Possibly	285
Asthma (493)	14	Most likely	218
Acute pharyngitis (462)	13	Possibly	613
Essential hypertension (401)	11	Definitely not	465

a Out of 861 diagnoses.

ICD-9-CM = International Classification of Diseases, 9th Edition–Clinical Modification.

Table III. Diagnosis codes with the highest odds ratios within atopic dermatitis/eczema patient claims compared with control population

Description (ICD-9-CM code)	Odds ratio	Expert opinion category	Prevalence rate (%)
Top 5 diagnoses by odds ratio			
Toxic effect, other metals (985)	9.82	Definitely not	0.004
Lichen – planus, nitidus, NOS (697)	7.74	Definitely not	0.187
Maternal complication affecting newborn (761)	7.36	Definitely not	0.011
Poisoning – CNS stimulants (970)	7.36	Definitely not	0.002
Other dermatoses (702)	7.04	Definitely not	0.475

ICD-9-CM = International Classification of Diseases, 9th Edition–Clinical Modification; **NOS** = not otherwise specified.

ries (9%) had an odds ratio less than 1.00. The data may have been skewed because AD/E is a chronic illness, and patients with chronic illnesses may be accessing the healthcare system at greater rates and with more confounding factors than patients with acute conditions. Another possibility is that patients with AD/E suffer from a chronic autoimmune disease with substantially wide-ranging (and perhaps under-recognised) comorbidities. Regardless of the explanation, this phenomenon may confound the finding that comorbidities ‘most likely’ and ‘possibly’ related to AD/E had generally high odds ratios, because the odds ratios for most ‘definitely not’ related conditions were also greater than 1.00.

One of the limitations of the original cost-of-illness study and this analysis is the reliance on diagnosis coding as supplied and processed through healthcare claims. Errors and omissions could have occurred at various clinical, coding, claims submissions and claims processing levels. Furthermore, patient disease severity, which might have a considerable impact on the presence of comorbid conditions was not available for evaluation as part of this study.

The focus of this study was to examine the validity of expert opinion when evaluated over the entire subset of comorbidities identified by the panel. The objective was not to examine the validity of any single comorbidity selected or disregarded by the expert panel with regard to its association with AD/E. Comorbidities associated with AD/E may have been overstated or unrecognised by the expert

panel. The existence of many ‘definitely not’ related data points near ‘most likely’ and ‘possibly’ related diagnoses in figure 2 suggests that the panel’s identification of comorbidities may not be 100% sensitive. Additional research on the actual ‘sensitivity’ of expert opinion by assessing the rate of ‘false negatives’ may be warranted, but is outside the scope of the current study. Development of methodologies to research further the relationship of other potential diseases to AD/E using epidemiological and other quantitative methods should be explored.

Conclusion

Our study has described a method to validate expert opinion regarding comorbidities associated with an individual disease. While its application to AD/E was the focus of this particular study, research efforts involving expert opinion in other disease areas can incorporate such methods to validate key assumptions, ensure more robust analyses and improve the generalisability and acceptance of results.

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