The Role of Ocular Perfusion Pressure in Glaucoma Cannot Be Studied With Multivariable Regression Analysis Applied to Surrogates

Ocular perfusion pressure (OPP) is not easily directly measurable, and the difference between blood pressure and intraocular pressure (IOP) has been suggested as a simple surrogate of OPP.\(^1\) We write in relation to publications in this journal\(^2\)-\(^5\) and elsewhere\(^4\) that have reported a significant association between OPP surrogates and glaucoma. We argue that these findings are based on incorrect interpretation of multivariable regression models, and that these simple surrogates cannot be used to examine the role of OPP in glaucoma. We illustrate this by theoretically reviewing the interpretation of coefficients in multivariable regression models, and then demonstrating the issue using a simulated dataset.

Interpretation of regression coefficients is straightforward in univariable regression. As an example, consider the setting of a cross-sectional study. A univariable logistic regression model examining whether IOP is associated with the prevalence of glaucoma would be as follows:

\[
\log(\text{odds of glaucoma}) = \alpha + \beta_1 \cdot \text{IOP} \quad (1)
\]

With IOP considered as a continuous variable, the interpretation of \(\beta_1\) would be the odds ratio (OR) for a diagnosis of glaucoma per mm Hg increase in IOP. Coefficient \(\alpha\) is the constant term and rarely presented or interpreted in analyses.

The interpretation of regression coefficients becomes more complicated in the setting of multivariable regression. Consider the situation of examining the association of both IOP and age with glaucoma:

\[
\log(\text{odds of glaucoma}) = \alpha + \beta_1 \cdot \text{IOP} + \beta_2 \cdot \text{age} \quad (2)
\]

The interpretation of \(\beta_1\) would now be the OR for glaucoma per mm Hg increase in IOP, \textit{holding IOP constant}. The last part of this interpretation is crucial, and this is what makes multivariable regression an effective method for adjusting for potentially important confounders.

Now consider the situation of examining the association between OPP surrogates and glaucoma. An example of an OPP surrogate is diastolic ocular perfusion pressure (DOPP), calculated from diastolic blood pressure (DBP) and IOP:

\[
\text{DOPP} = \text{DBP} - \text{IOP} \quad (3)
\]

To examine the association between DOPP and glaucoma, a univariable logistic regression model would be as follows:

\[
\log(\text{odds of glaucoma}) = \alpha + \beta_1 \cdot \text{DOPP} \quad (4)
\]

The interpretation of \(\beta_1\) is simply the OR for a diagnosis of glaucoma per mm Hg increase in DOPP.

In an attempt to determine if the association between DOPP and glaucoma is independent of IOP, some investigators have put both terms into the same multivariable regression model. For example:

\[
\log(\text{odds of glaucoma}) = \alpha + \beta_1 \cdot \text{DOPP} + \beta_2 \cdot \text{IOP} = \alpha + \beta_1 \cdot (\text{DBP} - \text{IOP}) + \beta_2 \cdot \text{IOP} \quad (5)
\]

Now the interpretation of \(\beta_1\) is not so simple. It is the OR for a diagnosis of glaucoma per mm Hg increase in DOPP, \textit{holding IOP constant}. If IOP is to be held constant, the only way for DOPP (\(= \text{DBP} - \text{IOP}\)) to increase is for the DBP component to increase. This means that \(e^{\beta_1}\) represents the OR for glaucoma per mm Hg increase in DBP, adjusted for IOP. It does not represent the OR per mm Hg increase in DOPP (a common misinterpretation; see below). Similarly, \(e^{\beta_2}\) represents the OR for glaucoma per mm Hg increase in IOP, while holding DOPP constant. This is equivalent to the OR per mm Hg increase in both IOP and DBP together. It does not represent the OR per mm Hg increase in IOP.

This phenomenon remains unchanged when other covariates are adjusted for, when using the open source programming

### Table 1. Results From a Multivariable Logistic Regression Model With Glaucoma Status as the Dependent Variable and DOPP and IOP as Continuous Explanatory Variables

<table>
<thead>
<tr>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOPP, mm Hg</td>
<td>1.005655</td>
<td>0.978898</td>
</tr>
<tr>
<td>IOP, mm Hg</td>
<td>1.259948</td>
<td>1.126622</td>
</tr>
</tbody>
</table>

\(\text{CI}, \text{confidence interval.}\)
that the unadjusted association between MOPP/SOPP/DOPP and incident glaucoma remained even when the blood pressure component of MOPP/SOPP/DOPP was replaced with random values. Furthermore, after they repeated the process 30 times (with different sets of random values), the magnitudes of association were largely distributed within the 95% confidence interval of the original hazard ratio. This strongly suggests that it is the IOP component of the perfusion pressure measurement that drives any significant association with glaucoma in unadjusted models, certainly within the Rotterdam cohort.

In summary, the strength of IOP as a risk factor for glaucoma precludes any useful interpretation of OPP surrogates (blood pressure – IOP) in unadjusted analyses, and adjusting for IOP changes the interpretation of regression coefficients such that they no longer reflect risk attributed to the perfusion pressure measure. Is it time to abandon the use of this type of surrogate measure of OPP? At the very least, the current interpretation of findings is confused and does not appear to be furthering the understanding of glaucoma.

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