Perinatal Factors Impact Neonatal Outcomes in HIE

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Background

Hypoxic-ischemic encephalopathy (HIE) is a disease with considerable neonatal morbidity and mortality. The disease has an incidence ranging from 2 to 9 per 1000 term births and presents as neonatal encephalopathy and seizures in term or late preterm infants (35 weeks or greater estimated gestational age). Clinically, these infants often have a difficult birthing process as reflected by low APGAR scores, significant acid/base derangements on umbilical cord blood gas measurement, and abnormal neurological exams at birth or shortly thereafter. Babies with mild HIE can be clinically observed, but cases with moderate to severe HIE require therapeutic hypothermia, ideally initiated within the first 6 hours of life and continued for a full 72 hours. Therapeutic hypothermia is thought to work by reducing metabolic stress to the fragile infant as well as decreasing oxygen free-radical damage, and it has been shown in the literature to improve developmental outcomes in these infants with a more significant phenotype of HIE.

A broad range of factors, both maternal and neonatal, has been associated with development of HIE. Any process negatively affecting the delivery of oxygen to the developing fetal/neonatal brain can be considered a potential precipitant of this disease. Often the underlying issue leading to HIE is reflected only indirectly through clinical surrogates. For example, fetal distress can be reflected by abnormal fetal heart tracing and meconium passage in utero – often with no clear cause. In other cases, the underlying issue is more obvious, such as in cases of a catastrophic uterine rupture or maternal placental abruption necessitating an emergent delivery. Still other cases seem to stem from difficulty with fetal extraction in the delivery process, as in the case of shoulder dystocia or fetal breech positioning. Whatever the presumed cause of the HIE, the results feed into a common pathway involving neonatal encephalopathy often accompanied by seizures. In the early newborn period, babies diagnosed with HIE can develop significant organ-system damage and can even die. Those that survive the initial hospitalization often will have developmental delay, cerebral palsy, or both.

Many studies have been performed examining factors that seem to lead to the development of HIE. However, there is a gap in the literature with respect to how these various factors might impact early neonatal outcomes. For example, do infants with history of fetal malpresentation do worse than those without? What about babies with documented abnormal heart rates prior to delivery? Lastly, once an infant is diagnosed with HIE, how does the development of a secondary issue like sepsis or hypoglycemia affect their outcome? This study attempts to delve into these and similar questions. I aim to examine the impact of various maternal and neonatal factors on early outcomes of infants with HIE, specifically 1) **neonatal morbidity** and 2) **neonatal mortality**. The morbidity outcome is difficult to measure directly but can be viewed obliquely using hospital length of stay as a surrogate. Mortality can be approached head-on. I hypothesize that different factors

associated with HIE exert differential effects on these outcomes, and that these differential effects can be measured (albeit imperfectly) and even predicted.

Methods

Study Design

I examined outcomes of neonatal mortality and neonatal intensive care unit (NICU) length of stay (LOS) for babies diagnosed with HIE. Neonatal mortality was defined as death during initial hospitalization after birth and LOS was considered to be the number of days during the initial hospitalization (no readmissions were considered).

To perform this analysis, I used the HCUP (Healthcare Cost and Utilization Project) 2012 Kids' Inpatient Database. The database provided information on demographic characteristics of infants, inpatient mortality, LOS, and diagnoses and procedures associated with each infant. The following variables were derived:

Variables Of Interest:

Variable	Type, # Levels	Description	ICD9 Codes Used (if applicable)
HIE	factor, 2	was neonate diagnosed with HIE	7680-7689, 34830, 34839, 77901
Race	factor, 4	white, black, hispanic, other	
Female	factor, 2	female?	
Hospital Region	factor, 4	Northeast, Midwest, South, West	
Insurance Payer	factor, 3	Medicaid, Private, Other	
C_section	factor, 2	born via c_section?	V3001
Fetal Heart Rate	factor, 2	abnormal heart rate during labor?	76381-76383
Hypoglycemia	factor, 2	was neonate ever diagnosed with hypoglycemia?	7756
Gestational Age	factor, 3	term, late preterm (35-36 weeks), postterm (42+ weeks)	76528-76529, 7662, 76621-76622
Seizures	factor, 2	was neonate ever diagnosed with seizures?	3450-34591, 7803-78039, 7790
Maternal Inflammatory Disease	factor, 2	did mother of patient have chorioamnionitis or premature rupture of membranes?	7627, 7611
Maternal Hypertension	factor, 2	was mother of patient diagnosed with hypertension affecting pregnancy?	7600

Fetal Malpresentation	factor, 2	was neonate's delivery affected by breech positioning or shoulder dystocia? (note: *these diagnoses are present in HCUP as "newborn affected by __" codes*)	7600
CPR	factor, 2	did infant require early CPR?	9960 (procedure)
Therapeutic Hypothermia	factor, 2	did infant receive early therapeutic hypothermia?	9981 (procedure)
Sepsis	factor, 2	did infant receive diagnosis of sepsis or serious bacterial infection? (note: *cases of observation for suspected infection deliberately excluded as these infants do not have true disease*)	77181, 7712,77189, 78552, 038-039, 99591-99592, 3202, 3229, 04149
LOS	continuous	length of initial inpatient stay (days)	
Death	factor, 2	did infant die during initial hospitalization?	

Conceptually, above variables (excluding the two outcome variables and the HIE variable itself, which forms the basis for the cohort) can be grouped into several overarching categories:

1. **maternal** factors (for example - maternal hypertension, maternal inflammatory disease)
2. **intrapartum** factors (for example - fetal malpresentation, abnormal fetal heart rate)
3. **neonatal** factors (for example - sepsis, need for therapeutic hypothermia, need for CPR)

It is important to remember that ALL of the neonates in the cohort I am considering had some form of HIE, but each differed in the balance of these various maternal, intrapartum, and neonatal factors. An attempt to measure the relative importance of the various factors in the outcomes of death and LOS forms the motivation for my analysis.

Table 1

factor	N_1	m_1
Race (uniform)	2,289	344
Indicator of sex	2,632	1
Region of hospital	2,633	0
Primary expected payer (uniform)	2,626	7

c_section	2,633	0
hypoglycemia	2,633	0
gest_age	2,633	0
seizure	2,633	0
mat_inflamm	2,633	0
HTN	2,633	0
malpresent	2,633	0
CPR_proc	2,633	0
hypothermia_proc	2,633	0
sepsis	2,633	0
Length of stay (cleaned)	2,633	0
Died during hospitalization	2,632	1

N_ ... #records used below, m_ ... #records not used

		Total
		N=2,633
Race (uniform)	White	1,194 (52.2%)
	Black	379 (16.6%)
	Hispanic	368 (16.1%)
	Other	348 (15.2%)
Indicator of sex	0	1,494 (56.8%)
	1	1,138 (43.2%)

Region of hospital	Northeast	455 (17.3%)
	Midwest	687 (26.1%)
	South	790 (30.0%)
	West	701 (26.6%)
Primary expected payer (uniform)	Medicaid	1,320 (50.3%)
	Private	1,093 (41.6%)
	Other	213 (8.1%)
c_section	0	1,973 (74.9%)
	1	660 (25.1%)
hypoglycemia	0	2,456 (93.3%)
	1	177 (6.7%)
gest_age	term	2,276 (86.4%)
	late preterm (35-36 weeks)	227 (8.6%)
	postterm	130 (4.9%)
seizure	0	1,825 (69.3%)
	1	808 (30.7%)
mat_inflamm	0	2,568 (97.5%)
	1	65 (2.5%)
HTN	0	2,604 (98.9%)

	1	29 (1.1%)
malpresent	0	2,526 (95.9%)
	1	107 (4.1%)
CPR_proc	0	2,540 (96.5%)
	1	93 (3.5%)
hypothermia_proc	0	2,430 (92.3%)
	1	203 (7.7%)
sepsis	0	2,108 (80.1%)
	1	525 (19.9%)
Length of stay (cleaned)		6 (2-11)
Died during hospitalization	0	2,504 (95.1%)
	1	128 (4.9%)

Data are presented as median (IQR) for continuous measures, and n (%) for categorical measures.

My study population was composed of newborns in the US diagnosed with HIE during their initial/birth hospitalization in the year 2012. I excluded all infants born before 35 weeks gestation, as whether such infants can even develop HIE is a matter of clinical debate. Any infants with metabolic disease were excluded, as well as infants with birth weight < 2000g. Additional exclusion criteria were neonatal coagulopathy, complex congenital heart disease, major congenital malformations, imperforate anus, suspected neuromuscular disorders, and known lethal chromosomal disorders. (*Note that the above are common exclusion criteria for neonatal therapeutic hypothermia.*) Of those infants who had received cooling therapy, I included both infants who started cooling therapy on day of birth and those who started the following day (in order to capture those born shortly before

midnight). For infants who had received CPR, an indicator of a very difficult delivery process, I used a similar include/exclude test.

In this analysis, I started with 05,902 neonates (representing all the neonates in the 2012 HCUP database with HIE, as described above). After the above exclusion criteria are applied, I was left with 02,633 neonates.

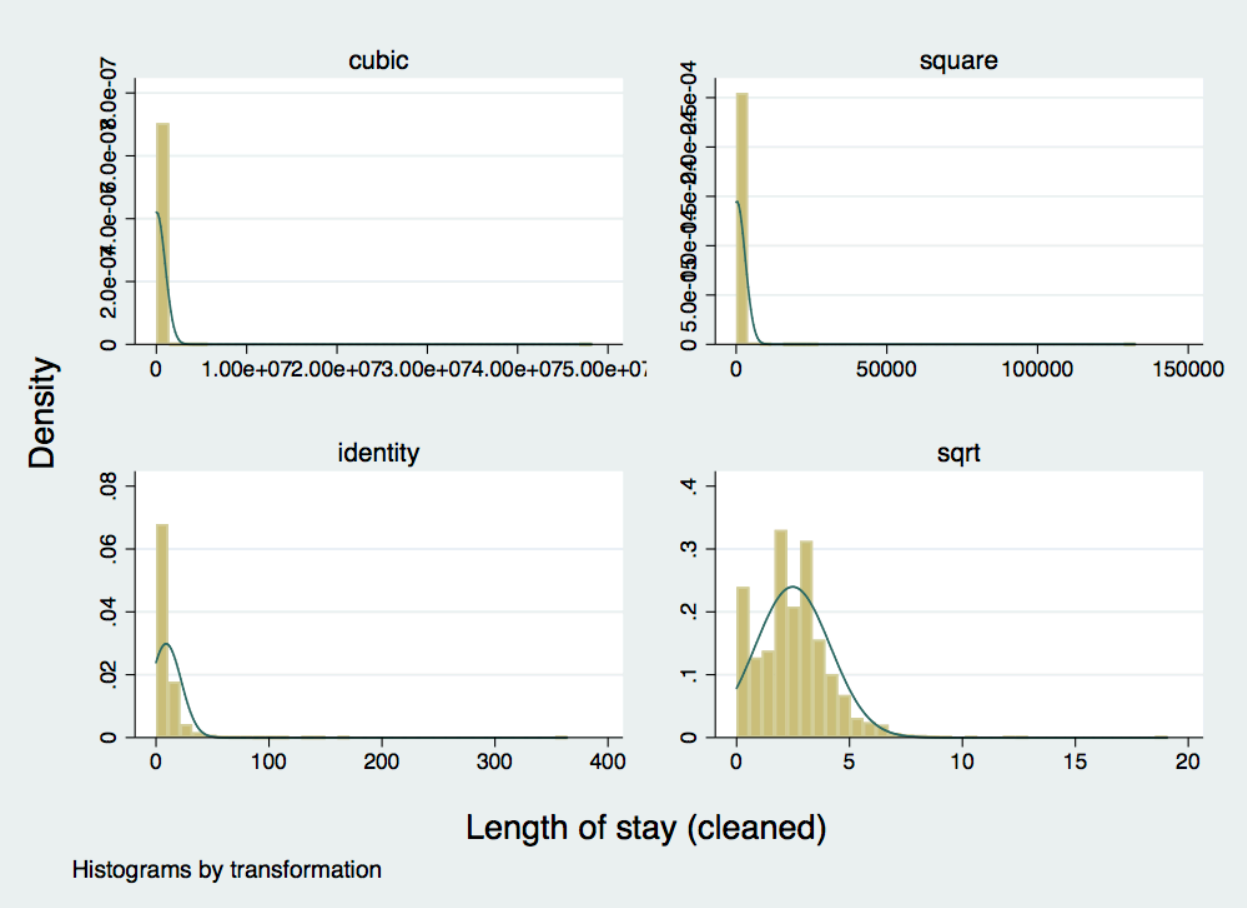
The primary outcomes were inpatient length of stay and patient death during hospitalization. LOS was calculated by subtracting admission date from discharge date.

Statistical Analysis

Regression modeling was performed to estimate inpatient LOS. Due to nonparametric distribution of LOS in the data, a square root transform of the LOS variable was used. As can be seen from the output below, this type of transformation normalized the data more effectively than the traditional log transform and thus was therefore a more appropriate choice.

```
Transformation         formula                chi2(2)       P(chi2)
─────────────────────────────────────────────────────────────────
cubic                  LOS^3                       .            .
square                 LOS^2                       .            .
identity               LOS                         .            .
square root            sqrt(LOS)                   .        0.000
log                    log(LOS)                    .            .
1/(square root)        1/sqrt(LOS)                 .            .
inverse                1/LOS                       .            .
1/square               1/(LOS^2)                   .            .
1/cubic                1/(LOS^3)                   .            .

(file gladderLOS.png written in PNG format)
```



gladder

Both standard linear multiple regression and robust regression approaches were used and performed similarly. Robust regression performed better on post-estimation analysis and was shown to conform more optimally to regression assumptions.

```
. gen sqrtLOS = sqrt(LOS)

. rreg sqrtLOS i.RACE FEMALE i.HOSP_REGION i.PAY1 fhr c_sec hypoglycemia
i.gest_age seizure mat_inflamm HTN
>  precip malpresent CPR_proc hypothermia_proc sepsis

   Huber iteration 1:  maximum difference in weights = .89319405
   Huber iteration 2:  maximum difference in weights = .10634901
   Huber iteration 3:  maximum difference in weights = .02828772
Biweight iteration 4:  maximum difference in weights = .29238337
Biweight iteration 5:  maximum difference in weights = .02830348
Biweight iteration 6:  maximum difference in weights = .00723342

Robust regression                               Number of obs     =      2,284
                                                F( 22,      2261) =      21.37
                                                Prob > F          =     0.0000
```

sqrtLOS	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
RACE						
Black	-.0227537	.0876692	-0.26	0.795	-.1946742	.1491668
Hispanic	.144497	.0907273	1.59	0.111	-.0334205	.3224145
Other	.0577114	.0869975	0.66	0.507	-.1128918	.2283146
FEMALE	-.0191173	.0596253	-0.32	0.749	-.1360434	.0978088
HOSP_REGION						
Midwest	.0203009	.0953513	0.21	0.831	-.1666844	.2072861
South	.0294836	.0875951	0.34	0.736	-.1422916	.2012588
West	.010544	.091278	0.12	0.908	-.1684534	.1895414
PAY1						
Private	-.1359991	.0661702	-2.06	0.040	-.2657598	-.0062384
Other	-.1844881	.1102512	-1.67	0.094	-.4006923	.0317161
fhr	-.3387607	.1837168	-1.84	0.065	-.6990319	.0215104
c_section	-.6017806	.0698845	-8.61	0.000	-.7388251	-.4647361
hypoglycemia	.177037	.1216586	1.46	0.146	-.0615371	.415611
gest_age						
late preterm (35-36 weeks)	.6955221	.105877	6.57	0.000	.4878958	.9031483
postterm	.0267551	.1375767	0.19	0.846	-.2430346	.2965449
seizure	.8139802	.0651135	12.50	0.000	.6862918	.9416686
mat_inflamm	.4740145	.1913336	2.48	0.013	.0988067	.8492222
HTN	.3719276	.2681713	1.39	0.166	-.1539601	.8978152
precip	-.4739595	.8130415	-0.58	0.560	-2.068345	1.120426

```
                malpresent |  -.1981125   .1504063    -1.32   0.188    -.4930613
.0968364
                  CPR_proc |  -.9645222   .1593099    -6.05   0.000    -1.276931
-.6521132
          hypothermia_proc |   .6555593   .1139893     5.75   0.000     .4320247
.8790939
                   sepsis |   .2194747   .0743616     2.95   0.003     .0736507
.3652988
                    _cons |   2.148553   .0960756    22.36   0.000     1.960147
2.336958
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------------
```

The model is statistically significant, with included terms explaining approximately 016% of the variation in square root of LOS.

Factors Significantly *Increasing* Neonatal LOS

Factor	coefficient
late preterm status	0.69552205
neonatal seizures	0.81398018
maternal inflammatory disease	0.47401447
therapeutic hypothermia	0.65555929
sepsis	0.21947473

Factors Significantly *Decreasing* Neonatal LOS

Factor	coefficient
private insurance	-.13599912
c-section	-.60178059
neonatal CPR	-.96452217

That the five factors listed above are associated with increased LOS make sense. A baby born late preterm by definition is a baby born a bit early, so it should not be surprising that that baby might need more time in the hospital. This is even more the case if that baby also has seizures or requires hypothermia, both of which indicate more profound neonatal encephalopathy. The fact that a baby who is septic, or has a risk factor for sepsis due to maternal inflammatory disease, would have an increased LOS is also not surprising.

The fact that receiving CPR shortly after birth *decreases* LOS, however, is a bit puzzling. We will come to see soon that neonatal CPR is significantly associated with mortality. If infants who receive CPR are sicker and thus die more often in the hospital, this does, unfortunately, decrease their length of stay. The other two factors decreasing LOS (c-section delivery and private insurance type) both make intuitive sense. C-section is less physically traumatic for the baby than a vaginal birth, and thus might require less time in the hospital. Patients with private insurance may be in the hospital a shorter time because they are overall healthier and/or receiving better care.

Next, I performed logistic regression for the binary outcome of inpatient neonatal death. Here is the model with all covariates included.

```
. logit DIED i.RACE FEMALE i.HOSP_REGION i.PAY1 fhr c_sec hypoglycemia i.gest_age
seizure mat_inflamm HTN m
> alpresent CPR_proc hypothermia_proc sepsis, or

note: mat_inflamm != 0 predicts failure perfectly
      mat_inflamm dropped and 56 obs not used

Iteration 0:   log likelihood = -449.86326
Iteration 1:   log likelihood = -437.85871
Iteration 2:   log likelihood = -411.02995
Iteration 3:   log likelihood = -410.61508
Iteration 4:   log likelihood = -410.60708
Iteration 5:   log likelihood = -410.60707

Logistic regression                               Number of obs     =      2,227
                                                  LR chi2(20)       =      78.51
                                                  Prob > chi2       =     0.0000
Log likelihood = -410.60707                       Pseudo R2         =     0.0873

------------------------------------------------------------------------------
             DIED | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------------+---------------------------------------------------------------
             RACE |
            Black |   1.409382    .393324     1.23   0.219     .8156034    2.435444
         Hispanic |   1.012686   .3372913     0.04   0.970     .5271919    1.945276
            Other |   1.265829   .3558083     0.84   0.402     .7296475    2.196023
                  |
           FEMALE |   1.005784   .2009519     0.03   0.977     .6798888    1.487893
                  |
       HOSP_REGION |
          Midwest |   .7975306   .2457442    -0.73   0.463     .4359789    1.458913
            South |    .977229   .2660636    -0.08   0.933     .5731197    1.666277
             West |   .5282937   .1687259    -2.00   0.046     .2825007    .9879418
                  |
             PAY1 |
          Private |   1.175325   .2724764     0.70   0.486     .7461452    1.851367
            Other |   2.500202   .7412376     3.09   0.002     1.398359     4.47025
```

```
                        |
                    fhr |   1.539091   .8994425     0.74   0.461     .4895797
4.838438
            c_section |   .5522254   .1451894    -2.26   0.024     .3298535
.9245101
         hypoglycemia |   1.258975   .4527125     0.64   0.522     .6222074
2.547411
                        |
              gest_age |
late preterm (35-36 weeks)  |   1.114894    .377739     0.32   0.748     .5739001
2.16586
            postterm  |    .652867      .3945    -0.71   0.480     .1997466
2.13388
                        |
                seizure |   1.696228   .3524718     2.54   0.011     1.128773
2.548952
           mat_inflamm |          1  (omitted)
                   HTN |   3.870207   2.236546     2.34   0.019      1.24691
12.0125
            malpresent |   .1082713   .1130973    -2.13   0.033     .0139756
.8387952
              CPR_proc |   8.919865   2.967105     6.58   0.000     4.647447
17.11993
      hypothermia_proc |   1.837157   .5936851     1.88   0.060     .9751625
3.461112
                sepsis |   1.850532   .4073576     2.80   0.005     1.202048
2.848863
                 _cons |   .0326539   .0104831   -10.66   0.000     .0174048
.0612637
------------------------+----------------------------------------------------
------------

Note: _cons estimates baseline odds.
```

Note that the output informs us that the variable pertaining to maternal inflammatory disease was dropped because it perfectly predicted "failure," (Stata's way of saying that this covariate actually predicted survival in each case). As each baby with maternal inflammatory disease survived in our dataset, Stata figures this variable is not helpful and drops it from the model.

```
. fitstat

Measures of Fit for logit of DIED

Log-Lik Intercept Only:     -449.863     Log-Lik Full Model:         -410.607
D(2201):                     821.214     LR(20):                       78.512
                                         Prob > LR:                     0.000
McFadden's R2:                 0.087     McFadden's Adj R2:             0.029
Maximum Likelihood R2:         0.035     Cragg & Uhler's R2:            0.104
McKelvey and Zavoina's R2:     0.175     Efron's R2:                    0.051
Variance of y*:                3.987     Variance of error:             3.290
Count R2:                      0.949     Adj Count R2:                  0.000
AIC:                           0.392     AIC*n:                       873.214
```

```
BIC:                        -16144.998     BIC':                          75.656

. estat gof

Logistic model for DIED, goodness-of-fit test

       number of observations =      2227
 number of covariate patterns =       958
            Pearson chi2(937) =       924.84
                  Prob > chi2 =         0.6051
```

The model is statistically significant, with included terms explaining approximately 08.7% of the variation in square root of LOS. The goodness of fit test demonstrates that our fit is satisfactory.

Factors Significantly Associated with *Increased* Mortality

Factor	coefficient (odds)
neonatal CPR	08.9198647
"other" insurance type	02.5002024
neonatal seizures	01.696228
maternal hypertension	03.8702071
sepsis	01.8505323

Factors Significantly Associated with *Decreased* Mortality

Factor	coefficient (odds)
hospital - West	0.5282937
C-section	0.55222538
malpresentation	0.10827127

From this, we see that receiving CPR in that first day of life is associated with greatly increased odds of death. This is probably not surprising, given that only the sickest babies will need CPR.

Discussion

Overall, late preterm status, presence of seizures, maternal inflammatory disease (defined as premature rupture of membranes and/or chorioamnionitis), neonatal sepsis, and receiving therapeutic hypothermia were all significantly associated with longer hospital stays for this cohort of infants with HIE. CPR significantly decreased length of stay, as did private insurance type and delivery by c-section.

Factors that significantly increased mortality were neonatal CPR, "other" insurance type (medicare, self-pay, or no charge patients), and being treated in a hospital in the Western part of the country. While hospital administrators in California may cheer this news, it was just barely significant and not likely to be meaningful.

As is always the case, this study has strengths and limitations. The results I obtained are hardly groundbreaking or surprising, but help move the needle in understanding the complex interplay of factors associated with prognosticating, as opposed to diagnosing, HIE in the immediate newborn period. The greatly increased odds of death with neonatal CPR clearly suggest that intrapartum factors (corresponding to the actual delivery process and delivery-room resuscitation for an infant) play a particularly critical role in the prognosis of infants with HIE. The study design benefits from the use of all-payer, HCUP data, which provides capture of a true, representative nationwide sample of infants.

Limitations of the study include reliance on ICD9 diagnosis and procedure codes, which can be inaccurate. The data did not contain useful patient-level information like APGAR score, cord blood gas results, or Sarnat staging which would have been helpful for understanding short-term outcomes in these patients. Additionally, the nature of HCUP data precluded obtaining long-term results like developmental outcomes for HIE patients.

My next step for this project will be to include other HCUP years, impute missing values, and to validate my results from this training sample. Once this is finished, I plan on working with my team of investigators at Cleveland Clinic to submit this for an abstract or poster and then ultimately a full manuscript publication.