INPLASY

Diagnostic and Prognostic Value of GLP-1 Receptor Expression in Neuroendocrine Tumors: A Systematic Review and Meta-Analysis

INPLASY202530091
doi: 10.37766/inplasy2025.3.0091
Received: 22 March 2025
Published: 22 March 2025

Jishu, JA; Limbach, KE; Fawzy, MS; Toraih, EA.

Corresponding author:
Eman Toraih

etoraih@tulane.edu

Author Affiliation:
Tulane University School of Medicine.

ADMINISTRATIVE INFORMATION

Support - No funding source.

Review Stage at time of this submission - Formal screening of search results against eligibility criteria.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202530091

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 22 March 2025 and was last updated on 22 March 2025.

INTRODUCTION

Review question / Objective What is the diagnostic accuracy of GLP-1R gene and protein expression in distinguishing neuroendocrine tumors from non-neuroendocrine neoplasms and normal tissues? Is GLP-1R expression associated with survival outcomes (overall survival and progression-free survival) in patients with neuroendocrine tumors?

Condition being studied Neuroendocrine tumors (NETs) and the expression of glucagon-like peptide-1 receptors (GLP-1Rs) in these tumors.

METHODS

Search strategy The following electronic databases will be searched: PubMed/MEDLINE, Embase, Web of Science, Cochrane Library, Scopus, Science Direct, Google Scholar, Genecards/NCBI.
The search will be conducted from database inception to March 1, 2025.

Search terms will include combinations of the following:
* "glucagon-like peptide-1 receptor," "GLP-1R," "GLP1R," "exendin-4"
* "neuroendocrine tumor," "NET," "neuroendocrine neoplasm," "NEN," "insulinoma," "gastrinoma," "carcinoid," "pheochromocytoma," "paraganglioma"
* "expression," "imaging," "diagnosis," "prognosis," "survival," "outcome"
Additional studies will be identified through the following:
* manual searches of reference lists from retrieved articles
* citation searching of included studies
* relevant review papers
* conference proceedings of major oncology and endocrinology meetings.

Participant or population The primary study populations to be studied are human patients of any age and gender with histologically confirmed neuroendocrine tumors of any primary site.

Intervention Assessment of GLP-1R expression in neuroendocrine tumor tissue or GLP-1R-targeted imaging using:
* immunohistochemistry (IHC)
* reverse transcription-polymerase chain reaction (RT-PCR)
* in vitro receptor autoradiography
* molecular imaging with radiolabeled exendin-4 derivatives or similar tracers
* other validated methods for receptor detection.

Comparator
For diagnostic studies:
* non-neuroendocrine neoplasms
* normal tissues
* other types of neuroendocrine tumors (for comparisons between subtypes)
For prognostic studies:
* low vs. high GLP-1R expression within NET patients.

Study designs to be included Observational studies (cross-sectional, case-control, cohort), prospective and retrospective studies, diagnostic accuracy studies, prognostic studies reporting survival outcomes, clinical trials reporting relevant diagnostic or prognostic data.

Eligibility criteria
Inclusion:
* human patients of any age and gender with histologically confirmed neuroendocrine tumors of any primary site
* studies including control groups (non-neuroendocrine neoplasms or normal tissues) for diagnostic accuracy assessment
Exclusion:
* animal studies
* in vitro studies without corresponding patient data
* studies with fewer than 10 patients.

Information sources PubMed/MEDLINE, Embase, Web of Science, Cochrane Library, Scopus, Science Direct, Google Scholar, Genecards/NCBI.

Main outcome(s)
Diagnostic performance:
* sensitivity
* specificity
* positive predictive value (PPV)
* negative predictive value (NPV)
* positive likelihood ratio (PLR)
* negative likelihood ratio (NLR)
* diagnostic odds ratio (DOR)
* area under the curve (AUC) of receiver operating characteristic (ROC) curves
Prognostic value:
* overall survival (OS)
* progression-free survival (PFS)
* disease-free survival (DFS)
* hazard ratios (HRs) with 95% confidence intervals.

Additional outcome(s)
* GLP-1R expression patterns across different NET subtypes
* correlation between GLP-1R expression and tumor grade
* correlation between GLP-1R expression and Ki-67 proliferation index
* differences in GLP-1R expression between primary tumors and metastases
* correlation between GLP-1R expression and functional status of the tumor
* performance of different GLP-1R detection methods
* correlation between GLP-1R expression and response to treatment.

Data management Two investigators will independently screen titles and abstracts, followed by full-text review of selected articles. Disagreements will be resolved through consensus or consultation with a third investigator.
Data extraction will be performed using a standardized form and will include:
1. Study characteristics (first author, publication year, country, study design, sample size)
2. Patient demographics (age, gender, tumor location, tumor grade, metastatic status)
3. GLP-1R assessment methodology (technique, antibody used for IHC, scoring system)
4. GLP-1R expression patterns (percentage of positive cells, staining intensity, cellular localization)
5. Imaging parameters (tracer used, scanning protocol, quantification method)
6. Diagnostic performance metrics (sensitivity, specificity, accuracy, PPV, NPV)
7. Prognostic outcomes (OS, PFS, HRs and 95% CIs, follow-up duration)
For studies reporting survival outcomes, hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) will be extracted. When HRs are not directly reported, they will be calculated from Kaplan-Meier curves.

Quality assessment / Risk of bias analysis The methodological quality of included diagnostic studies will be assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool, which evaluates risk of bias and applicability concerns across four domains: patient selection, index test, reference standard, and flow and timing.

For prognostic studies, quality assessment will be performed using the Newcastle-Ottawa Scale (NOS), which evaluates selection of study groups, comparability of groups, and ascertainment of exposure or outcome.
Two investigators will independently assess study quality, and disagreements will be resolved through discussion or consultation with a third investigator.

Strategy of data synthesis Diagnostic Performance Analysis:
Pooled estimates of sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) will be calculated using a bivariate random-effects model. Summary receiver operating characteristic (SROC) curves will be constructed, and the area under the curve (AUC) will be calculated to evaluate overall diagnostic accuracy.
Prognostic Value Analysis:
Pooled HRs with 95% CIs will be calculated using a random-effects model to assess the association between GLP-1R expression and survival outcomes (overall survival and progression-free survival).
Heterogeneity will be assessed using the I2 statistic and Cochran's Q test, with I2 values of 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively.
If sufficient data are available, meta-regression and subgroup analyses will be performed to explore potential sources of heterogeneity.

Subgroup analysis
Subgroup analyses will be performed based on:
1. Tumor location (pancreatic NETs vs. gastrointestinal NETs vs. pulmonary NETs vs. other sites)
2. Tumor grade (G1 vs. G2 vs. G3/NEC according to WHO classification)
3. Functional status (functional vs. non-functional)
4. GLP-1R assessment method (IHC vs. RT-PCR vs. in vitro autoradiography)
5. GLP-1R-targeted imaging tracer (^{68}Ga-labeled vs. ^{18}F-labeled vs. other radiolabeled exendin-4 derivatives)
6. Study design (prospective vs. retrospective)
7. Sample size (50 patients)
8. Publication year (before 2015 vs. 2015 and later).

Sensitivity analysis As mentioned above, sensitivity will be calculated using a bivariate random-effects model. Summary receiver operating characteristic (SROC) curves will be constructed, and the area under the curve (AUC) will be calculated to evaluate overall diagnostic accuracy.

Language restriction English only.

Country(ies) involved USA, Egypt, Saudi Arabia.

Keywords Neuroendocrine tumors; GLP-1 receptor; diagnostic biomarker; prognostic biomarker; meta-analysis; systematic review.

Dissemination plans Results will be disseminated through publication in a peer-reviewed scientific journal, presentation at relevant international conferences, and sharing with appropriate research networks and professional organizations.

Contributions of each author
Author 1 - Jessan Jishu.
Author 2 - Kristen Limbach.
Author 3 - Manal Fawzy.
Author 4 - Eman Toraih.